DISSOCIATION OF SENSORIMOTOR DEFICITS AFTER ROSTRAL VS.
CAUDAL LESIONS IN THE PRIMARY MOTOR CORTEX HAND
REPRESENTATION

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Running Title: Somatosensory Deficits After M1 Lesions

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ABSTRACT

Primary motor cortex (M1) has traditionally been considered a motor structure. While neurophysiologic studies have demonstrated that M1 is also influenced by somatosensory inputs (cutaneous and proprioceptive), the behavioral significance of these inputs has yet to be fully defined in primates. The present study describes differential sensory-related deficits following small ischemic lesions in either the rostral or caudal subregion of the M1 hand area in a non-human primate. Squirrel monkeys retrieved food pellets out of different sized wells drilled into a Plexiglas board. Before the lesion, monkeys retrieved pellets by directing the hand to the well, inserting fingers directly into it, and extracting the pellet. After a lesion to the rostral portion of M1, monkeys frequently failed to direct the hand accurately to the well. Instead, fingers contacted the surface of the board outside the well before entering the well. These aiming errors are consistent with both the large amount of proximal motor outputs and the predominant proprioceptive inputs of rostral M1. Overall, these aiming errors are suggestive of dysfunctional processing of proprioceptive information, or the failure to integrate proprioceptive information with motor commands. In contrast, after a lesion to the caudal portion of M1, monkeys frequently examined their palm visually for the presence of the pellet after an attempted retrieval. These errors are consistent with both the large amount of distal motor outputs and the
predominant cutaneous inputs of caudal M1. Thus, these errors are suggestive of a deficit in processing of cutaneous information, or the failure to integrate cutaneous information with motor commands. Rostral and caudal M1 lesions result in different deficits in sensory-dependent motor control that appear to correlate with broad segregation of motor outputs and previously described sensory inputs of M1.

Key words: recovery, rehabilitation, sensorimotor integration, somatosensory, stroke
INTRODUCTION

Primary motor cortex (M1) has traditionally been considered a motor structure since low-level electrical stimulation of M1 results in contraction of skeletal muscles. Corticospinal neurons reside in layer V of M1 and project to the spinal cord, where they synapse mono- and di-synaptically onto motoneurons. M1 also has well-known connections with other motor areas such as premotor and supplementary motor cortex (Godshalk et al., 1984; Stepniewska et al., 1993). It has been known since at least the early 1950s (Malis et al., 1953) that M1 also receives somatosensory input, predominantly from the ventrolateral and ventral posterolateral nuclei of the thalamus (Horne and Tracey, 1979; Lemon and Van Der Burg, 1979; Asanuma and Mackel, 1989; Holsapple et al., 1991; Shindo et al., 1995) and somatosensory cortex (Jones and Powell, 1968; Yumiya and Ghez, 1984; Porter and Sakamoto, 1988; Stepniewska et al., 1993; Tokuno and Tanji, 1993; Caria et al., 1997). The structure, organization, and function of sensory inputs to motor cortex have been studied extensively, especially in cats. The cat motor cortex receives its primary somatosensory inputs from the ventrolateral (VL) nucleus of the thalamus (Asanuma and Mackel, 1989). Additionally, somatosensory area 2 of the cat projects to motor cortex and appears to be important in motor skill learning (Jones and Powell, 1968; Porter and Sakamoto, 1988).
Based on neuroanatomic connections and neurophysiologic response properties, the M1 hand area appears to be segregated into caudal (M1c) and rostral (M1r) subregions. In non-human primates, M1c has been shown to be connected primarily with areas 3a, 1, the second somatosensory cortex (S2) and the parietal ventral area (PV), and to a lesser extent areas 2 and 3b and the ventral premotor cortex (PMV), while M1r is connected primarily with areas 2, S2, dorsal premotor cortex (PMD), PMV, and to a lesser extent areas 1, 3a, and posterior parietal cortex areas 5 and 7b (Stepniewska et al., 1993). Intracortical microstimulation studies in the squirrel monkey have shown that the M1c hand area contains predominantly digit and wrist representations. However, the M1r hand area also contains proximal representations (elbow, shoulder) that are interspersed with distal representations (Donoghue et al., 1992; Nudo et al., 1997). Neurons responding to cutaneous stimulation are segregated to the M1c forelimb representation while neurons responding to proprioceptive stimulation are largely segregated to M1r, although some proprioceptive responses can be recorded throughout the hand representation (Rizzolatti et al., 1981; Tanji and Wise, 1981; Strick and Preston, 1982; Picard and Smith, 1992a, b; Nudo et al., 1997; Boudreau and Smith, 2001). Cutaneous receptive fields in M1 are considerably larger than analogous receptive fields in somatosensory area 3b (Tanji and Wise, 1981; Strick and Preston, 1982; Humphrey et al., 1994). Cutaneous and proprioceptive inputs have also been identified in M1 of humans using fMRI
(Moore et al., 2000), though submodality segregation within M1 may be beyond the spatial resolution of current fMRI techniques. Additional functional, anatomical, and neurochemical differences between the M1r and M1c subregions have been described in humans (Geyer et al., 1996). Somatosensory intracortical projections to motor cortex have been shown to be important in motor skill learning (Jones and Powell, 1968; Pavlides et al., 1993). After motor cortex lesions, animals exhibit decreased motor skill on manual tasks (Ogden and Franz, 1917; Kennard, 1936; Denny-Brown, 1950; Travis, 1955; Castro-Alamancos and Borrell, 1993; Castro-Alamancos and Borrel, 1995; Hoffman and Strick, 1995; Nudo et al., 1996a; Friel and Nudo, 1998; Rouiller et al., 1998). However, relatively little attention has been given to changes in sensory aspects of motor control after lesions confined to M1. To examine the effects of focal inactivation of cat motor cortex on reaching and grasping movements, Martin et al. (1993) injected a GABA$_A$ agonist, muscimol, into either rostral or caudal subdivisions. Both injections resulted in slowed movements, but rostrolateral M1 inactivation uniquely caused integrative deficits in aiming of the paw (hypermetria) and impaired use of somatosensory cues and deficits in adaptive control (Martin and Ghez, 1991; Martin et al., 1993). Caudal M1 inactivation did not impair performance until much later, when the muscimol may have spread to the rostral portion of M1. Thus, due to the differential connections of rostral and caudal M1 (Yumiya and Ghez, 1984), lesions to different parts of motor cortex
may result in specific deficits in sensorimotor integration, and possibly the integration of proprioceptive cues and visual information regarding the location of the target (Martin et al., 1993). These results suggest that rostral and caudal M1 may play different roles in sensorimotor integration required for skilled movements. Sensorimotor impairments may correspond with the segregation of sensory input to M1.

Because motor outputs (Donoghue et al., 1992; Nudo et al., 1997) and proprioceptive and cutaneous inputs (Tanji and Wise, 1981; Strick and Preston, 1982) are, to some extent, segregated in the primate M1, similar dissociation of deficits should be produced by focal lesions in monkeys. Thus, the present study was conducted to assess sensory, or sensory-dependent motor deficits in reaching and grasping behavior after lesions confined to either the rostral or caudal portion of the M1 hand representation in squirrel monkeys. The results demonstrate that aiming errors, similar to hypermetria in cats, result from lesions in primate rostral M1, i.e., the region receiving primarily proprioceptive input. Another type of sensory-dependent deficit, similar to a sensory agnosia seen after somatosensory cortex lesions (Randolph and Semmes, 1974), results from lesions in primate caudal M1, i.e., the region receiving predominantly cutaneous input. These findings are likely due to the differential distribution of motor outputs and somatosensory inputs in M1.
MATERIALS AND METHODS

Subjects

Eight adult squirrel monkeys, six males and two females, \((\text{Saimiri spp.}; 600\text{ to }1200\text{ grams})\) were used in the present study. All procedures were approved by the University of Kansas Medical Center’s Institutional Animal Care and Use Committee. Each of the eight monkeys underwent the identical behavioral and neurophysiological procedures except for the exact site of the ischemic injury (see below). The monkeys are identified as subjects 1 through 4 in the caudal lesion group and 5 through 8 in the rostral lesion group.

The general procedures were conducted in the following order: 1) hand preference testing; 2) prelesion motor training and behavioral assessment; 3) neurophysiologic mapping and cortical lesion; 4) post-infarct behavioral training and assessment. These procedures are described in detail below.

Hand Preference Testing

The hand preference of each animal was determined by testing on a modified Klüver board, a \(24\times7.6\times1.8\text{ cm}\) rectangular Plexiglas apparatus containing five 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 (Figure 1). Wells were in full view at all times. Monkeys were able to look between the cage bars and see each well clearly. This apparatus is identical to that used in previous studies in this laboratory for examining hand use in squirrel monkeys (Friel and Nudo, 1998). Hand preference testing consisted of 50 trials per day for two consecutive days. Each trial began when a 45 mg food pellet (Bio-Serv, Frenchtown NJ) was placed randomly into one of the five wells. Each trial ended when the monkey retrieved the pellet and brought it inside the cage. During each trial, all food wells were visible to the monkey, as is the animal's hand. All trials were recorded using a video camera (Sony Hi-8).

To determine hand preference, videotapes of trials were reviewed using a Hi-8 videocassette editing deck. The hand used in each reach was tallied, and the hand used in over 50% of successful retrievals was considered the dominant hand (Nudo et al., 1992).

**Prelesion Training and Baseline Assessment Procedures**

After hand preference was determined, each animal was fitted with a mesh jacket that had a mesh sleeve enclosing the nondominant arm (Figure 1). The sleeve was closed at the distal end, constraining the animal from using its nondominant hand to retrieve pellets from the Klüver board. The
animal was able to use this arm for climbing and balance. The sleeve was used to encourage the animals to use the dominant hand exclusively during prelesion and postlesion training.

One to two days after the monkey was fitted with the jacket, prelesion training began. Two training sessions were conducted daily, one in the morning, one in the afternoon. The evening before each session, food was removed from the cage. Each session consisted of 25 probe trials followed by 30 min of training. In each probe trial, a food pellet was placed into one well and the monkey retrieved the pellet. The order of wells used was randomly assigned for each probe trial. Five trials were conducted in each of the five wells (randomized block design).

After the probe trials were completed, pellets were placed into a training well. Pellets were presented as rapidly as they were retrieved. The training session ended after 30 min or after the monkey failed to retrieve a pellet after five minutes. On the first day of training, the largest well was the training well. On the following days, the training well, or wells, was determined using the monkey's performance on the previous day. If the monkey retrieved a predetermined high criterion (HC) number of pellets from the training well, the next smallest well was used as the training well on the following day. If the monkey did not retrieve the HC number of pellets, but retrieved more pellets than a predetermined low criterion (LC), the training well did not change on the following day. If the monkey retrieved a number of pellets
lower than the LC, on the following 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 two consecutive days. Monkeys required an average of 23.6 ± 8.9 days to complete 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 two consecutive days on the smallest well, random probe trials were conducted over the next two days. Each day, two sessions of 50 trials were conducted.

All probe trial and training sessions were videotaped. Random probe trials on the final two days were used to define baseline performance (see below).

_Intracortical Microstimulation Methods_

Within three days after prelesion training was complete, animals were sedated with ketamine (Fort Dodge Animal Health, Fort Dodge IA), 20 mg/kg i.m. The trachea was intubated and the saphenous vein was catheterized. During the entire procedure, body temperature was maintained using a
homeothermic blanket system and respiration rate, CO₂ output, heart rate, and blood oxygen saturation were continuously monitored. Monkeys were placed into a stereotaxic frame and were given a mixture of nitrous oxide (750 ml/hr), oxygen (250 ml/hr) and halothane (1.5-3%) anesthetic. Under sterile conditions, a 1.5 cm² portion of skull over the precentral gyrus containing the hand representation of primary motor cortex (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 silicone oil (Applied Silicone Corp., Ventura CA) warmed to 38°C.

After the surgical opening was complete, nitrous oxide/halothane anesthesia was withdrawn, and ketamine (20 mg/kg/hr) combined with acepromazine (Fort Dodge, Fort Dodge IA; 0.01 mg/kg/hr) or diazepam (Roche Laboratories, Nutley NJ; 0.01 mg/kg/hr) was used for anesthesia during the neurophysiologic mapping procedure. The alkylphenol anesthetic propofol (Abbot Laboratories, Chicago IL, 15 mg/kg/hr iv) was used in one case (9652) during mapping because a stable anesthetic state could not be maintained with ketamine/acepromazine or ketamine/diazepam in that animal.

A photograph of the exposed cortex (and calibration bar) was taken with a digital camera and imported into a graphics program (Canvas v3.5 for Mac, Deneba, Miami FL). A 250 µm² grid was superimposed onto the photo of cortex. At each grid crosspoint, a 3.5 M NaCl-filled glass electrode, with a tip diameter of 10-25 µm and an impedance of 400-1000 kΩ, was inserted.
perpendicular to the cortex to a depth of 1700-1800 μm using a micropositioner. A series of 40 ms current trains consisting of thirteen 200 μs monophasic cathodal pulses (300 Hz) was then delivered at a rate of 1/s by a constant-current stimulator. If a grid crosspoint marked an area over a blood vessel, the electrode was introduced into the cortex as close as possible to the grid coordinate while avoiding the blood vessel. At each site, current was gradually increased from zero until a joint movement was evoked (maximum of 30 μA). The current was increased a few microamps to verify the evoked movement. Then the current was gradually reduced until the response was visible during 50% of the pulse trains. This current level was defined as the threshold current, and the evoked movement was documented. 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 300-350 sites and took 10-15 hours to derive. Because the cerebral cortex of squirrel monkeys is relatively unconvoluted, the entire M1 hand area is exposed on an unfissured sector, allowing accurate derivation of two-dimensional topographic maps.
Cortical Lesion Procedure

After the motor map was completed, ketamine/acepromazine or ketamine/diazepam anesthesia was withdrawn, and halothane/nitrous oxide anesthesia was given. Based on the neurophysiologic mapping data, the distal forelimb (or hand) representation (the area consisting of digit, wrist and forearm representations) was arbitrarily divided into rostral and caudal halves for the purpose of lesion creation. While neurophysiologic procedures to more precisely define zones receiving primarily cutaneous (caudal) vs. proprioceptive (rostral) afferents have been used in this laboratory previously, we used a more arbitrary method to define the rostral/caudal border for the following reasons: 1) Microstimulation mapping procedures are more reliable in defining the full extent of the M1 hand area, and thus are necessary for these studies. 2) Sensory mapping during the same surgical procedure would require a considerably longer period under anesthesia, potentially compromising the animal’s recovery. 3) Previous studies of submodality segregation in M1 suggested that the cutaneous/proprionicceptive border is roughly located at 1/3 to 1/2 of the distance from the caudal limit to the rostral limit of the M1 hand area as defined by microstimulation mapping (Tanji and Wise, 1981; Nudo et al., 1997). A cortical lesion involving 30-45% of the total M1 hand representation was produced within the rostral or caudal half of the hand representation (Figure 2). The lesion was targeted to the largest contiguous region of digit representations within the rostral/caudal half of the
map. However, since digit, wrist, and forearm representations within M1 are interspersed (Donoghue et al., 1992; Nudo et al., 1997), it was not possible to restrict the lesion exclusively to digit representations.

Surface blood vessels supplying the targeted area of cortex were permanently occluded using microforceps connected to a bipolar coagulator. This method has been found to produce restricted ischemia and subsequent necrosis through all layers of cortex, avoiding white matter. The size of the lesions, and the survivability of adjacent tissue is precise and reproducible (Nudo and Milliken, 1996; Nudo et al., 1996a). After the ischemic lesion was made, the exposed cortex was observed for 30-60 min to monitor potential reperfusion of any blood vessels that had been occluded. If any reperfusion was observed, the blood vessel was re-cauterized. Once it was decided that significant reperfusion was not likely to occur, the brain was covered with gelfilm (Upjohn, Inc., Kalamazoo MI), the bone flap was cemented in place with dental acrylic (Lang; Wheeling IL), and the skin sutured. Local anesthetic (lidocaine; Abbot Laboratories, Chicago IL) was applied to the incised skin. The animal was then removed from the halothane/nitrous oxide anesthesia, and then from the stereotaxic frame, and placed in a temperature controlled recovery chamber. When the monkey was fully alert and active (12 to 24 hours), it was returned to its home cage.

Postlesion Testing Procedure
Following the infarct, two days of probe trials (50 trials/day) were conducted over the first two days that the animal was able to perform pellet retrievals (typically days 3-6 post-infarct) to assess the impact of the lesion.

After the postlesion hand preference had been documented, monkeys were fitted with a jacket that restrained the arm ipsilateral to the lesion (same arm that was restricted prelesion). Thus, the monkeys were required to use their impaired hand to retrieve pellets. The postlesion testing procedure was identical to the prelesion training procedure (probe trials on all wells, followed by testing on one well for 30 min., see above). Monkeys required an average of 26.3 ± 6.3 days to complete postlesion testing.

**Histological Procedure**

After the postlesion training procedure was complete, animals were deeply anesthetized with a lethal dose of Euthasol (Delmarva Labs, Inc., Midlothian VA) and perfused with 0.9% phosphate-buffered saline followed by 4% phosphate-buffered paraformaldehyde fixative. In some cases, the brain was removed and motor cortex was cut into 50 µm parasagittal sections. The area 3a/4 border was defined cytoarchitectonically and the location of the lesion was verified. In previous studies in this laboratory, this cytoarchitectonically defined border has been shown to be well correlated with the neurophysiologically defined border of M1 based on intracortical
microstimulation at a maximum current of 30μA (Nudo and Milliken, 1996). Thus, these histological results are not repeated here.

This histological procedure was useful in verifying that the lesion extended through all layers of cortex, but cannot be used to accurately define the extent of the lesion. After several weeks’ survival following the lesion, substantial necrosis and scavenging of the tissue within the lesion occurs. Therefore, less direct methods were used to estimate lesion size. Prelesion and postlesion digital photographs were used to estimate lesion area. Immediately after the lesion was made, the damaged cortex became blanched in color. The lesion could be easily seen in one-month postlesion photographs. Postlesion photographs of intact vasculature were superimposed onto prelesion photographs, enabling the determination of the cortical territory spared by the lesion. Using these estimation methods, the areal extent of the cortical surface destroyed by the lesion (in mm²) was estimated (Friel and Nudo, 1998; Friel et al., 2000). Photographs of M1 before and one month after a lesion are shown in Friel et al., 2000. The size and extent of lesions are highly reproducible, verified neurophysiologically, and re-verified in subsequent mapping studies (Nudo and Milliken, 1996; Nudo et al., 1996a; Friel and Nudo, 1998; Frost et al., 2003; Plautz et al., 2003). Additionally, in some cases laser Doppler measurements of infarcted tissue immediately following the lesion, one hour post lesion, and one month post lesion have verified the location and permanence of the lesions. Laser
Doppler measurements have been shown to accurately identify the lesion (Frost et al., 2003).

**Analysis of Motor Performance**

Videotapes of probe trial sessions during the prelesion and postlesion periods were examined in slow motion on a Hi8 videocassette editing deck (Sony). Probe trials, rather than training trials, were used in the analysis since probe trials were conducted on every well, each day, while training trials were conducted on only 1-2 wells per day. Several measures of motor performance were tallied:

*Finger flexions per retrieval* was defined as the total number of times the monkey flexed its fingers while the fingers were in the testing well, divided by the total number of successful retrievals. Finger flexions per pellet retrieval were averaged for each day of testing. Although data were collected from all five testing wells, results from the smallest well are presented (10 trials/day), since retrieval from the smallest well required the greatest skill, and resulted in the greatest postlesion deficits. Motor deficits were not evident on the largest well after the lesion.

**Motor Performance Index**: Finger flexions per retrieval over the two testing days before the lesion were averaged to yield a baseline measure of prelesion motor performance for each animal. Daily postlesion finger flexions per retrieval for each animal were divided by that animal’s baseline finger
flexions per retrieval to generate a normalized motor performance index (MPI).

Duration of retrieval was defined as the time beginning when the distal tip of the monkey's hand crossed through the plane parallel to the cage bars toward the Klüver board until the time the distal tip of the monkey's hand crossed the plane parallel to the cage bars when the hand was retracted into the cage after a successful retrieval. Duration of retrieval was measured in milliseconds every other day for ten probe trials on the smallest well. Duration of retrieval data were collected from a sample of trials during the periods from two to five days before the lesion and from one to 30 days after the lesion.

Assessment of Somatosensory-Related Deficits

Cutaneous sensory error: Videotapes of probe trials from all wells were reviewed in slow motion. A cutaneous sensory error was defined as an event in which the animal failed to grasp the pellet, but removed its hand from the testing well, brought the hand to or near the mouth, and then visually inspected the empty palm. An example of a cutaneous sensory error is shown in the supplementary video file frielcutaneous.mov. An example of a normal retrieval is shown in the supplementary video file frielnormal.mov. These errors are tentatively called cutaneous sensory errors here because they are similar to errors made after somatosensory cortex lesions in monkeys, and possibly clinically related to a type of sensory agnosia.
(Pavlides et al., 1993; Xerri et al., 1998). Subsequent to such an error, the monkey typically reached back into well and made additional attempts to retrieve the pellet. It was possible for the monkey to make more than one cutaneous sensory error per trial. A trial was defined as one successful pellet retrieval. Errors per trial were computed for each day of testing.

**Aiming error frequency:** Videotapes of probe trials from all wells were reviewed in slow motion. An aiming error was defined as an event in which the animal reached toward the well and touched the top surface of the Klüver board with its fingers before inserting them into the well. A trial was defined as one successful pellet retrieval. An example of an aiming error is shown in the supplementary video file frielaiming.mov. Errors per trial were computed for each day of testing.

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*Determinación de la localización de la lesión relativa*

Maps of the M1 hand representation have irregular shapes (Figure 2). Also, the shape and size of the M1 hand representation is highly variable between individual animals (Nudo et al., 1992; Nudo et al., 1996b; Plautz et al., 2000). Thus, to quantify the location of the lesion in the M1 hand representation in a standard way a measure of relative lesion location was defined for the present study.
First, the rostral-caudal length of the hand representation was measured and the midpoint identified. Then the distance from the rostral border of the hand representation to the lesion midpoint was measured. The relative lesion location was determined using the following equation:

Relative lesion location = Distance from rostral border of map to lesion midpoint / Rostral-caudal length of map

The computed value was a number between zero and one, with values near zero being located more rostrally and values near one being located more caudally.

Statistical Analyses

Since behavioral performance in an individual animal was often quite variable from day to day, daily behavioral measures were averaged to yield the weekly motor performance index, duration of retrieval, cutaneous sensory error rate, and aiming error rate. ANOVA was used to compare all weeks and Fisher's LSD post-hoc statistical measures were computed to determine group differences in behavioral results by week.

Nonparametric correlation analyses (Spearman Coefficient) were performed to test the correlation of each behavioral measure on week 1 post-lesion with the relative location of the lesion. Analyses were restricted to week 1 postlesion because the most marked behavioral deficits were seen in week 1. Parametric analyses (Z-test) were performed to test the correlation
of each behavioral measure on week 1 post-lesion with the size of the lesion
and size of the representational areas destroyed by the lesion. These two
different tests were used to test the correlation of behavioral measures to a
relative measure (relative location of the lesion; Spearman Coefficient) and to
absolute measures (flexions per retrieval, cutaneous sensory error, aiming
error; Z-test).
RESULTS

Motor performance before and after lesion

Changes in the motor performance index (MPI) on the smallest well after an M1c lesion are shown in Figures 3a-b. Daily MPI results were pooled into five weeks. Figure 3a summarizes average data by week. Analysis of variance indicated a significant effect of week (F = 4.29, p = 0.018). During the first week after the lesion, the MPI increased significantly beyond prelesion performance (p = 0.003; Fisher’s PLSD), indicating a decline in skill. During the second week after the lesion, the MPI returned to the normal range (p = 0.290). During the third week after the lesion, the MPI again increased significantly beyond the prelesion measure, indicating a decline in skill (p = 0.037). During the fourth week after the lesion, the MPI again returned to the normal range (p = 0.737). Figure 3b depicts daily data for an individual animal. Three of the four animals in the M1c lesion group showed a 2-3 fold increase in MPI in the first week after the lesion; for the fourth animal, MPI increased by 56%. Two of the four animals displayed a significant relapse in motor skill during postlesion week 3. By postlesion week 4, all MPI measures had returned to near-prelesion levels. Changes in the MPI after an M1r lesion are shown in Figures 3c-d. Figure 3c summarizes average data by week. Analysis of variance indicated that there was no significant effect of week on the MPI (F = 2.58, p = 0.091). During the four
weeks after the lesion, the MPI remained within the normal range for each animal. Figure 3d depicts daily data for an individual animal. Figure 4a summarizes average **duration of retrieval** by week, measured in milliseconds, after a caudal lesion. Analysis of variance indicated a significant effect of week ($F = 5.50, p = 0.010$), roughly paralleling the pattern seen for the MPI. During the first week after the lesion, the retrieval duration increased significantly beyond prelesion performance time ($p = 0.004$; Fisher’s PLSD). During the second week after the lesion, the retrieval duration returned to the normal range ($p = 0.468$) and remained within the normal range during the third and fourth weeks postlesion. Figure 4b depicts data for an individual animal. Changes in the duration of retrieval after a rostral M1 lesion are shown in Figures 4c-d. Figure 4c summarizes average data by week. Analysis of variance indicated that there was no effect of week on the duration of retrieval ($F = 0.28, p = 0.885$). During the four weeks after the lesion, the duration of reach remained within the normal range for each animal. Figure 4d depicts data for an individual animal.

**Somatosensory-related deficits before and after lesion**

**Cutaneous sensory errors:** Daily measures of cutaneous sensory errors per trial on all wells were grouped by week. Since most of the prelesion values were near zero, the distribution of data was not normal. Thus, nonparametric analyses were performed on the data.
Changes in the cutaneous sensory error rate after an M1c lesion are shown in Figure 5a-b. There was a statistically significant effect of week on cutaneous sensory error rate (H = 13.5, P = 0.009; Kruskal-Wallis). Before a caudal lesion, monkeys rarely made cutaneous sensory errors. During the first week after the caudal lesion, all monkeys made many cutaneous sensory errors, an average of 1.53 errors per pellet retrieval. This was significantly greater than the prelesion error rate (q = 3.5, p<0.005; Tukey post-hoc analysis). The cutaneous sensory error rate was no longer statistically significant during week 2 postlesion and remained statistically indistinguishable from the prelesion error rate through week 4 postlesion.

Changes in the cutaneous sensory error rate after an M1r lesion are shown in Figure 5c-d. There was not a statistically significant effect of week on cutaneous sensory error rate (H = 2.6, P = 0.635; Kruskal-Wallis). Before the lesion, monkeys rarely made cutaneous sensory errors. After the rostral lesion, the cutaneous sensory error rate remained within prelesion levels. For one animal in the M1r group, the cutaneous error rate increased from 0.05 errors/trial to 0.17 errors per trial after the lesion (monkey 4). Incidentally, the lesion in this animal was located more caudally (yet still confined to the rostral half of M1) than the other animals in this group. The cutaneous sensory error rate for the other three animals in this group did not change after the rostral lesion.
**Aiming deficits**: Changes in the aiming error rate on all wells after an M1c lesion are shown in Figure 6a-b. There was not a statistically significant effect of week on aiming error rate ($H = 3.24$, $P = 0.198$). Before a caudal lesion, monkeys rarely made aiming errors. During the first week after the M1c lesion, aiming error rate increased to 0.24 errors per trial, although this increase was not statistically significant due to high individual variability. Of the four animals in this group, one showed a large increase in aiming errors (rate of 0.67 errors per trial, monkey 5), while two made aiming errors at a rate of approximately 0.1 errors per trial (monkeys 6 and 7). The fourth animal made no aiming errors after the lesion (monkey 8). During weeks two through four after the M1c lesion, the aiming error rate remained within prelesion levels.

Changes in the aiming error rate after an M1r lesion are shown in Figure 6c-d. There was a statistically significant effect of week on aiming error rate ($H = 13.5$, $P = 0.009$). Before an M1r lesion, monkeys rarely made aiming errors. During the first week after the M1r lesion, monkeys made an average of 0.27 errors per trial. This was significantly greater than the prelesion error rate ($q = 2.8$, $p<0.05$). Each of the animals in the M1r lesion group showed a 10- to 30-fold increase in the number of aiming errors after the lesion. During the second week after the M1r lesion, monkeys made an average of 0.20 errors per trial. This rate approached statistical significance ($q = 2.7$, $p<0.051$). The aiming error rate returned to prelesion levels during
week 3 postlesion and remained within normal range through week 4 postlesion.

**Group Comparison of Lesion Size**

The relative lesion size was calculated by dividing the absolute lesion size (in mm\(^2\)) by the absolute size of the hand representation (in mm\(^2\)). There were no statistical differences between the groups with respect to either the absolute (t = 1.53, p = 0.177) or relative (t = 1.78, p = 0.125) lesion size.

**Group Comparison of Quantitative Measures of Lesion Location**

By definition, lesions in the M1r vs. M1c lesion groups were made in different physical locations within the M1 hand representation. Since, in many animals, M1r and M1c contained different proportions of digit, wrist/forearm, and proximal representational area, comparisons of the areas of specific movement representations contained within the lesion were made between the M1r and M1c lesion groups. Table 1 summarizes the areal contents of the lesion in each group of animals. The proportion of the lesion containing digit, wrist/forearm, and proximal representational areas is summarized for each case in Table 2. Lesion location was measured by the area of representation within the lesion (in mm\(^2\)) and by the proportion of the lesion containing a representation. Representational areas within the lesion were
defined as the prelesion motor mapping responses derived within the area that was later destroyed by the lesion.

Statistically significant differences were found between the two groups with respect to the absolute and proportional amount of digit (p < 0.0001) and wrist/forearm (p < 0.02) representational area in the lesion. There was a statistically significant difference in the proportional amount of proximal area in the lesion between the two groups (p = 0.034), and the difference between the two groups with respect to the absolute amount of proximal representational area destroyed by the lesion approached statistical significance (p = 0.051). Thus, M1c lesions involved relatively more digit, but less wrist/forearm and less proximal representations compared with M1r lesions. This variable stemming from the normal distribution of movement representations within the M1 hand area is considered in detail in the Discussion section.

Relationship Between Behavioral Deficits and Lesion Size

The technique used to make lesions in the present study allows for lesions to be targeted to a very specific location within the M1 hand representation. Although this technique is very precise, there was small, though not statistically significant variability in the sizes of the lesions in different groups of animals, due to individual variability in vascular patterns in
M1 (M1c - 45.5% ±15.5%, M1r - 30.2% ± 5.3% relative lesion size; t = 1.79, p > 0.16).

Relationship Between Behavioral Deficits and Quantitative Measures of Lesion Location

Since these experiments demonstrate different behavioral deficits in groups of animals that received an M1r vs. an M1c lesion, correlation analyses were performed to determine the relationship between the location of the lesion and postlesion behavioral measures. Lesion location was measured in two different ways: 1) the relative position of the lesion on the rostral/caudal axis (see Materials and Methods), i.e. the physical location of the lesion, and 2) the areas of specific movement representations contained within the lesion, i.e. the functional location of the lesion.

Correlations between relative lesion location and behavioral measures are shown in Figure 7. The week 1 postlesion average of three different behavioral measures—motor performance index, cutaneous sensory errors per trial, and aiming errors per trial—are plotted against the relative lesion location measurement. The Spearman Correlation between each behavioral result and the relative lesion location was calculated. There was a statistically significant correlation between the relative lesion location and the week 1 postlesion motor performance index (Z = 2.14, p = 0.032, R = 0.81). More rostral lesions resulted in a smaller motor deficit after
the lesion, while more caudal lesions resulted in a larger motor deficit after the lesion.

There was also a statistically significant correlation between the relative lesion location and the average week 1 postlesion cutaneous sensory error rate ($Z = 2.14, p = 0.032, R = 0.81$). More rostral lesions resulted in fewer cutaneous sensory errors per trial, while more caudal lesions resulted in a greater number of cutaneous sensory errors per trial. The correlation between the relative lesion location and the average week 1 postlesion aiming error rate was not statistically significant ($Z = -1.26, p = 0.208 R = -0.48$).

A second analysis of lesion location, i.e., the functional location of the lesion, was performed to determine a possible relationship between the amount of representational area of specific joints destroyed by the lesion and behavioral deficits. Table 3 shows the correlations between behavioral deficits and the amount of digit, wrist/forearm, proximal, and wrist/forearm + proximal (non-digit) representational area destroyed by the lesion. Significant correlations were found between week 1 motor performance index and the absolute amounts of digit ($p = 0.037$) and non-digit ($p = 0.005$) representational area in the lesion. Significant correlations were also found between week 1 motor performance and the proportion of the lesion containing digit ($p = 0.005$) and non-digit ($p = 0.002$) areas. That is, performance was worse in monkeys with more digit and less non-digit area in
the lesion. Significant correlations were also found between cutaneous sensory error rate and the proportion of the lesion containing digit (p = 0.037) and non-digit (p = 0.023). That is, cutaneous sensory error rate was greater in monkeys with more digit and less non-digit area in the lesion. No significant correlations were found between week 1 aiming error rate and wrist/forearm, proximal, or combined wrist/forearm + proximal representational areas. The proportion of the lesion containing digit, wrist/forearm, and proximal areas for each monkey are summarized in Table 2.

Since lesions in the two groups of animals contained different amounts of digit and wrist/forearm representational area (Table 1), correlations were performed between functional lesion location and behavioral outcomes within groups to assess the correlation between the two measures independent of group differences, although the n per group is low (n=4). Z-scores and significance values are summarized in Table 4. Within the M1c lesion group, there were no statistically significant correlations between the proportions of any movement representation contained in the lesion with behavioral deficits. Within the M1r lesion group, there were no statistically significant correlations between the proportions of digit representations contained in the lesion with week 1 postlesion motor performance. There were significant correlations between the proportion of wrist/forearm and proximal representations contained in the lesion with week 1 postlesion motor performance. There
were no statistically significant correlations between the proportions of any movement representation contained in the lesion with aiming or cutaneous sensory deficits.
DISCUSSION

The present study in non-human primates provides evidence that the M1 hand representation can be divided into rostral (M1r) and caudal (M1c) subregions based upon differential behavioral effects of focal lesions. The behavioral dissociation appears to be correlated with at least two properties of M1 organization: 1) the segregation of cutaneous and proprioceptive inputs to M1c and M1r, respectively, as reported in other studies (see below) and 2) the prevalence of sites in M1c at which electrical stimulation evokes movement of digits, as opposed to movements of wrist, forearm and shoulder.

Structural and functional segregation within primary motor cortex (M1) has long suggested that the M1r and M1c subregions may serve somewhat different functions. Because in most primate species, M1c is buried in the anterior bank of the central sulcus, selective injury or inactivation has rarely been attempted. However, observations of M1 stroke patients (Schieber, 1999; Kim, 2001) and M1 inactivation in monkeys (Kubota, 1996; Schieber and Poliakov, 1998; Brochier et al., 1999; Fogassi et al., 2001) have demonstrated that caudal inactivation results in selective deficits in individuation of finger movements and relative preservation of reaching.

In certain South American primates, such as the squirrel monkey (and owl monkey), the fronto-parietal cortex is relatively smooth and unfissured.
The central sulcus is quite shallow (1-2 mm), and typically lies immediately caudal to the M1 hand representation. This species provides an excellent model to dissociate the effects of M1r and M1c lesions in detail.

*Differential Behavioral Deficits After M1r or M1c Lesions in Squirrel Monkeys*

In the present study, M1c lesions resulted in an increase in the motor performance index (MPI), indicating a decrease in manual motor skill. M1c lesions also resulted in an increased duration of retrieval. Monkeys displayed a behavior suggestive of a cutaneous sensory deficit. That is, monkeys visually inspected the palm during a pellet retrieval, strikingly similar to observations in monkeys after somatosensory cortex lesions (Randolph and Semmes, 1974; Pavlides et al., 1993; Xerri et al., 1998). M1c lesions did not result in any statistically significant increase in aiming error rate during the entire month of postlesion rehabilitative training.

After M1c lesions, the MPI increased beyond prelesion levels in week 1, then returned to prelesion levels in week 2. In week 3, the MPI relapsed to beyond prelesion levels before returning to prelesion levels in week 4. This motor skill relapse was seen in two of the four animals and has been discussed in a previous study (Nudo et al., 1996a). A similar relapse has been seen after M1 lesions in the rat. Motor maps shrink during the time of the relapse in the rat and expand again after the relapse (Goertzen et al.,
The mechanisms by which the motor skill relapse occurs and resolves are not understood.

In contrast to M1c lesions, after M1r lesions, neither the MPI nor the duration of retrieval changed significantly. There was also no statistically significant change in cutaneous sensory error rate. However, monkeys displayed a significant increase in aiming error rate. The negligible change in the MPI or the duration of retrieval in monkeys with M1r lesions appears counter-intuitive since the size of the lesions in the two groups was similar (and was in fact larger in the M1r group). However, the monkeys typically made aiming errors by over-reaching. The fingers were then pulled back over the surface of the board to be inserted into the well. The time to accomplish a retrieval using this strategy only minimally affected reach retrieval times.

Aiming and cutaneous sensory error rates returned to normal levels a few weeks after an M1r or M1c lesion, respectively. It is possible that monkeys quickly adopt compensatory strategies that enable them to retrieve pellets efficiently, despite a sensory-related motor deficit (Friel and Nudo, 1998). One plausible mechanism of compensation could be the use of visual feedback. Based upon anecdotal observations, we suspect that monkeys gradually come to rely more heavily on visual guidance in the pellet retrieval task during the course of recovery. As recovery progressed, monkeys tended to look at the training well and their hand during pellet retrieval. Monkeys
may rely heavily on visual information to assist in the accurate placement of
the hand in the well and/or in verification that the pellet has been retrieved.

*Previous Studies Demonstrating Differential Behavioral Effects of Lesions in
Motor Cortex*

Deficits in reaching and grasping after motor cortex lesions have also
been demonstrated in the cat. Martin and Ghez (1993) identified differences
in cat reaching behavior after rostral vs. caudal M1 inactivations. All
inactivations increased movement time and produced postural changes.
Rostrolateral inactivation produced hypermetric aiming errors, grasping
deficits, and an inability to correct reach trajectories to avoid an obstacle.
Rostromedial inactivation produced hypometric aiming errors, likely a
consequence of muscle weakness, but not grasping impairments or deficits in
trajectory adaptation. Caudal inactivation did not discernibly impair aiming,
grasping, or trajectory adaptation immediately after the inactivation. The
authors attribute these differences to differences in the distribution of
representational territory of different muscle groups; i.e. more proximal
representations in the rostral areas, and suggest that rostrolateral motor
cortex may be an important site for processing and integrating sensorimotor
information. The present study supports this hypothesis.

The present study demonstrates a characteristic behavioral deficit after
lesions to caudal M1. Such a deficit was not found in the cat (Martin and
Ghez, 1993), possibly due to anatomical differences between cats and monkeys. Both cat and monkey paws possess glabrous pads, but the cat paw possesses much more hair than the squirrel monkey hand. It is possible that cats did not demonstrate cutaneous sensory errors after caudal M1 inactivations because hair receptors may have provided additional sensory cues during retrieval. Additionally, the target food reward in the cat studies was much larger, relative to the size of the cat paw, than the target pellets used in the present study, relative to the size of the monkey hand. Larger food rewards would provide a greater area of sensory activation on the paw, including hairy skin, potentially providing sufficient sensory feedback for the cat to detect the presence of the food in the paw. Thus, the results from caudal M1 inactivations (Martin and Ghez, 1993) and the present results are not incongruous, but may rather reflect differences in the animal models used.

**Relationship Between Differential Behavioral Effects of Lesions and Motor Output Organization**

The present results indicate that in prelesion motor maps in this study, M1c contained proportionately more area devoted to digit movements compared with M1r; M1r contained more area devoted to wrist/forearm and proximal representations. Thus, the proportion of digit area contained in the lesion was positively correlated with the motor performance index and
cutaneous sensory error rate between lesion groups. The proportion of wrist/forearm area contained in the lesion was negatively correlated with the cutaneous sensory error rate.

It is possible that the different behavioral effects of rostral vs. caudal lesions are, at least in part, due to the differences in amount of digit, wrist/forearm, and proximal representational area destroyed by the lesion. Perhaps caudal lesions result in manual motor deficits because caudal lesions destroy a greater proportion of digit area than rostral lesions. Conversely, rostral lesions produce aiming deficits because rostral lesions destroy a greater proportion of wrist, forearm, elbow and shoulder area, a hypothesis that was suggested in a previous cat study (Martin and Ghez, 1993). Additionally, motor cortical activity associated with finger movements appears to be greatest in caudal M1 (Lemon et al., 1986; Lemon et al., 1990). Long-duration microstimulation of M1c in macaques produces complex grasping movements suggestive of feeding movements (Graziano et al., 2002).

Relationship Between the Differential Behavioral Effects of Lesions and Segregation of Somatosensory Afferents in M1

The effects of small lesions in M1 appear to be correlated with the distribution of motor outputs. However, one additional attribute of M1 organization, the distribution of cutaneous and proprioceptive inputs,
potentially contributes to this relationship. Cutaneous sensory information appears to be very important for efficient pellet retrieval on the task used in the present study. Lesions to the cutaneous hand representation in somatosensory area 3b in owl and squirrel monkeys have been shown to result in a manual performance deficit on the identical pellet retrieval task as that used in the present study (Xerri et al., 1998). Since cutaneous sensory information is conveyed to the M1c, it is not unexpected that destruction of M1c would result in deficits in tasks requiring digital contact and skilled manipulation of objects.

In addition, M1c also receives some proprioceptive input. It is noteworthy that the mean aiming error rate for the M1c lesion group was nearly as high as that of the M1r lesion group during week 1 postlesion. However, the error rate was not statistically different from prelesion levels due to high individual variability in the M1c group. Thus, it is possible that a larger group of animals would demonstrate aiming errors after M1c lesions. Also, in the present study, rostral-caudal boundaries were arbitrarily assigned based on previous sensory mapping experiments in M1 in this species indicating that cutaneous responses were restricted to the caudal one-third to one-half of the M1 hand area (Humphrey et al., 1994). Individual variability in somatosensory submodality distributions within M1 may account for some of the variability in postlesion error rates. Notably, the animal in the M1c group
that had the most rostral lesion of the group (monkey 5) also had the highest aiming error rate.

Likewise, M1r lesions destroy cortical tissue that receives predominantly proprioceptive, but little cutaneous input. Thus, after an M1r lesion, aiming error rate increased significantly, while cutaneous sensory error rate did not change. The M1r lesions in this study presumably did not destroy cutaneous sensory receptive fields in M1. This may account for the failure of M1r lesions to cause a motor performance deficit in the present study. It is likely that M1r lesions would cause a larger performance deficit on a task that required more accurate skilled aiming.

Two additional observations suggest that the different behavioral deficits of rostral vs. caudal lesions are, at least in part, due to different sensory properties of M1r and M1c. First, the cutaneous sensory errors observed in this study are very similar to those seen after lesions confined to the area 3b hand area. Such deficits have been likened to sensory agnosias that occur in humans (Randolph and Semmes, 1974; Xerri et al., 1998). Second, within the M1r or M1c lesion groups, there was not a correlation between the amount of digit or proximal representational area with the number of cutaneous sensory or aiming errors.

Conclusion
The present study provides evidence that M1 plays an important role in sensorimotor integration. Pure M1 lesions resulted in behavioral deficits that are indicative of sensorimotor deficits and that generally correlate with both the segregation of motor outputs and somatosensory submodality inputs of the M1 hand representation. These two properties of M1 organization are difficult to disentangle. It is possible that other squirrel monkeys might have a more balanced digit distribution in M1r and could be used to examine this issue further in future studies. Further, if in future studies both somatosensory and motor information in M1 is derived in detail, it may be possible to use statistical methods to partial out the relative contributions of these two factors.
ACKNOWLEDGMENTS

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REFERENCES


rat is due to the reorganization of adjacent areas of cortex.

Neuroscience 68:793-805.


Figure 1: Squirrel monkey retrieving food pellets from a Klüver board well. The monkey wore a jacket with a black mesh sleeve over the nondominant arm (arrow; arm hidden in shadows). This jacket allowed the animal to complete the task only with its dominant hand.
Figure 2. Location of ischemic lesions in M1 hand area. A: Representative lesion in caudal portion of M1 hand area. B: Representative lesion in rostral portion of M1 hand area. In each case, intracortical microstimulation techniques were used to define the topography of distal forelimb movement representations in M1. A bipolar electrocoagulator was used to permanently occlude surface vasculature within a restricted rostral or caudal zone in M1. Photographs of surface vasculature depicted here were taken prior to the microstimulation mapping procedure. Colored dots indicate the location of a microstimulation penetration. Stimulation was conducted at ~1750μm below the surface (layer V), using currents ≤ 30μA. Colors indicate movement evoked using threshold current levels. Red = digit; green = wrist or forearm; red+green = digit + wrist/forearm; blue = elbow or shoulder; black = no
response at 30μA. Yellow outline indicates boundary of hand representation (i.e., digit, wrist, and forearm). Black outline indicates proximal representations embedded within hand representation. Red outline indicates location of ischemic lesion. Following occlusion of surface vasculature, the tissue within the targeted area became blanched, and eventually was reduced in size due to necrosis. Non-responsive sites along the caudal boundary of the M1 hand representation typically correspond to area 3a (Nudo and Milliken, 1996). M: medial; C: caudal.
Figure 3: Motor performance before and after an M1 lesion. The motor performance index was the number of finger flexions per pellet retrieval divided by the prelesion flexions per retrieval in each monkey.  

A. Motor performance in weekly epochs before and after a lesion in M1c. Performance was significantly poorer during weeks 1 and 3 postlesion relative to prelesion levels (* - p<0.05; ** - p<0.01).  

B. Daily motor performance for one representative animal before and after a lesion in M1c.  

C. Motor performance in weekly epochs before and after a lesion in M1r. Motor performance did not change significantly.  

D. Daily motor performance for one representative animal before and after a lesion in M1r.
Figure 4: Duration of retrieval before and after an M1 lesion. A. Duration of retrieval in weekly epochs before and after a lesion in M1c. Duration was significantly greater during week 1 postlesion relative to prelesion levels (* - p<0.05; ** - p<0.01). B. Daily duration of reach for one representative animal before and after a lesion in M1c. C. Time of reach in weekly epochs before and after a lesion in M1r. Time of reach did not change significantly. D. Daily time of reach for one representative animal before and after a lesion in M1r.
Figure 5: Cutaneous sensory errors per trial before and after an M1 lesion.

A. Cutaneous sensory error rate in weekly epochs before and after a lesion in M1c. Error rate was near zero before the lesion, but increased significantly during week 1 postlesion, then returns to baseline levels during weeks 2 through 4 postlesion (** - p<0.01). B. Daily error rate for one representative animal before and after a lesion in M1c. C. Cutaneous sensory error rate in weekly epochs before and after a lesion in M1r. Error rate was near zero before lesion and did not significantly increase during the postlesion period. D. Daily error rate for one representative animal before and after a lesion in M1r.
Figure 6: Aiming errors per trial before and after an M1 lesion. A. Aiming error rate in weekly epochs before and after a lesion in M1c. Error rate was near zero before the lesion and did not increase during the postlesion period. B. Daily error rate for one representative animal before and after a lesion in M1c. C. Aiming error rate in weekly epochs. Error rate was near zero before a lesion in M1r. During week 1 postlesion, aiming error rate was statistically higher than the prelesion error rate. During week 2 postlesion, aiming error rate was nearly significantly different than the prelesion error rate. Aiming error rate returned to baseline levels during the weeks 3 and 4 after (* - p<0.05; † - p<0.051). D. Daily error rate for one representative animal before and after a lesion in M1r.
Figure 7: Correlations between relative lesion location and behavioral measures. Numbers above the data points denote the case from which the data was derived. A. Correlation between the week 1 postlesion motor
performance index and the relative lesion location. There was a statistically
significant correlation between the two measures (p<0.033). B. Correlation
between the week 1 postlesion cutaneous sensory error rate and the relative
lesion location. There was a statistically significant correlation between the
two measures (p<0.033). C. Correlation between the week 1 postlesion
aiming error rate and the relative lesion location. There was not a statistically
significant correlation between the two measures (p>0.2).
Supplementary video files:

Frielnormal.mov: Four successful pellet retrievals from a normal animal after prelesion training.

Frielcutaneous.mov: An example of cutaneous sensory errors in an animal four days after a caudal M1 lesion.

Frielaiming.mov: An example of aiming errors in an animal seven days after a rostral M1 lesion.
**Table 1: Lesion Locations**

<table>
<thead>
<tr>
<th></th>
<th>Caudal Lesion Group</th>
<th>Rostral Lesion Group</th>
<th>Statistical Comparison</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Range</td>
<td>S.D.</td>
</tr>
<tr>
<td><strong>Amount of representational area in lesion (mm²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit</td>
<td>2.32</td>
<td>2.00-2.82</td>
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<td>Wrist/forearm</td>
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<td>0.06-0.26</td>
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<td><strong>Proportion of lesion containing representational area</strong>*</td>
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<tr>
<td>Digit</td>
<td>0.72</td>
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<tr>
<td>Proximal</td>
<td>0.05</td>
<td>0.02-0.08</td>
<td>0.03</td>
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</tbody>
</table>

* Since some lesions contained nonresponsive area, the proportion of lesion containing digit, wrist/forearm, and proximal area does not add to 1.
Table 2: Proportion of lesion containing representational areas

<table>
<thead>
<tr>
<th>Case #</th>
<th>Digit</th>
<th>Wrist/Forearm</th>
<th>Proximal</th>
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<tr>
<td></td>
<td></td>
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<td>Rostral lesion group</td>
</tr>
<tr>
<td>1</td>
<td>0.12</td>
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<td>0.13</td>
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<td>2</td>
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<td>0.10</td>
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<td>0.41</td>
</tr>
<tr>
<td>4</td>
<td>0.14</td>
<td>0.58</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Caudal lesion group</td>
</tr>
<tr>
<td>5</td>
<td>0.81</td>
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<td>0.02</td>
</tr>
<tr>
<td>6</td>
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<td>0.02</td>
<td>0.05</td>
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<tr>
<td>7</td>
<td>0.63</td>
<td>0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>8</td>
<td>0.72</td>
<td>0.11</td>
<td>0.05</td>
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</tbody>
</table>
Table 3: Correlations between lesion location and behavioral deficits

Cell values indicate results of Z-test on measures in corresponding row vs. column.

<table>
<thead>
<tr>
<th>Amount of representation in lesion</th>
<th>Average Week 1 Postlesion Values</th>
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<tr>
<td></td>
<td>Motor performance index</td>
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<tr>
<td>Digit</td>
<td>Z = 2.07; p = 0.037</td>
</tr>
<tr>
<td>Wrist/forearm</td>
<td>Z = -1.75; p = 0.081</td>
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<tr>
<td>Proximal</td>
<td>Z = -1.76; p = 0.078</td>
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<tr>
<td>Wr/forearm + proximal</td>
<td>Z = -2.83; p = 0.005</td>
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<td>Proportion of lesion containing representation</td>
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<tr>
<td>Digit</td>
<td>Z = 2.79; p = 0.005</td>
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<tr>
<td>Wrist/forearm</td>
<td>Z = -1.53; p = 0.126</td>
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<tr>
<td>Proximal</td>
<td>Z = -1.86; p = 0.061</td>
</tr>
<tr>
<td>Wr/forearm proximal</td>
<td>Z = -3.09; p = 0.002</td>
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</table>
Table 4: Correlations between lesion location and behavioral deficits within groups

Cell values indicate results of Z-test on measures in corresponding row vs. column

<table>
<thead>
<tr>
<th></th>
<th>Caudal Lesion Group</th>
<th>Rostral Lesion Group</th>
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<tr>
<td></td>
<td>Week 1 Postlesion Average</td>
<td>Week 1 Postlesion Average</td>
</tr>
<tr>
<td></td>
<td>Motor Performance Index</td>
<td>Cutaneous Sensory Error Rate</td>
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<tr>
<td></td>
<td></td>
<td>Z = 0.14; p = 0.888</td>
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<td>Z = -0.06; p = 0.956</td>
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<tr>
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<td>Z = 0.99; p = 0.323</td>
<td>Z = 0.30; p = 0.767</td>
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<tr>
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<td>Z Value</td>
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