Reorganization of Remote Cortical Regions After Ischemic Brain Injury: A Potential Substrate for Stroke Recovery


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Frost, S. B., S. Barbary, K. M. Friel, E. J. Plautz, and R. J. Nudo. Reorganization of remote cortical regions after ischemic brain injury: a potential substrate for stroke recovery. J Neurophysiol 89: 3205–3214, 2003; 10.1152/jn.01143.2002. Although recent neurologic research has shed light on the brain’s mechanisms of self-repair after stroke, the role that intact tissue plays in recovery is still obscure. To explore these mechanisms further, we used microelectrode stimulation techniques to examine functional remodeling in cerebral cortex after an ischemic infarct in the hand representation of primary motor cortex in five adult squirrel monkeys. Hand preference and the motor skill of both hands were assessed periodically on a pellet retrieval task for 3 mo postinfarct. Initial postinfarct motor impairment of the contralateral hand was evident in each animal, followed by a gradual improvement in performance over 1–3 mo. Intracortical microstimulation mapping at 12 wk after infarct revealed substantial enlargements of the hand representation in a remote cortical area, the ventral premotor cortex. Increases ranged from 7.2 to 53.8% relative to the preinfarct ventral premotor hand area, with a mean increase of 36.0 ± 20.8%. This enlargement was proportional to the amount of hand representation destroyed in primary motor cortex. That is, greater sparing of the M1 hand area resulted in less expansion of the ventral premotor cortex hand area. These results suggest that neurophysiologic reorganization of remote cortical areas occurs in response to cortical injury and that the greater the damage to reciprocal intracortical pathways, the greater the plasticity in intact areas. Reorganization in intact tissue may provide a neural substrate for adaptive motor behavior and play a critical role in postinjury recovery of function.

INTRODUCTION

Cortical injury, as might occur in stroke, is frequently found to affect the initiation and execution of muscular contraction in the extremities opposite the side of the injury. In particular, fine manipulative abilities and skilled use of the upper extremity are often degraded (Bucy 1944; Hoffman and Strick 1995). In the weeks and months after injury, a gradual return of some motor abilities occurs (Lashley 1924; Travis and Woolsey 1956), although complete recovery of function is rare in humans (Gowland 1987).

There is mounting evidence that the return of function observed after cortical injury is largely attributable to adaptive plasticity in the remaining cortical and subcortical motor apparatus (Chollet et al. 1991; Liepert et al. 2000). In the search for neural substrates for adaptive plasticity, studies to date have focused on cortical motor structures adjacent to the site of injury. For example, both neurophysiologic and neuroanatomic studies in experimental animals (Jenkins and Merzenich 1987; Nudo and Miliken 1996) and both neuroimaging and noninvasive stimulation studies in humans (Cao et al. 1994; Cramer et al. 1997; Traversa et al. 1997; Weiller and Rijntjes 1999) confirm functional, seemingly adaptive alterations in the healthy tissue immediately adjacent to a cortical infarct. These examples of adaptive plasticity are consistent with a long-held belief that functions lost due to cortical injury may be “taken over” by tissue immediately adjacent to the injury (Black et al. 1970).

In addition, a large number of reports, especially from the clinical literature, point to functional alterations in more distant motor structures, either in the same hemisphere as the injury or in the opposite hemisphere (Cao et al. 1998; Nelles et al. 1999; Seitz et al. 1998). Reorganization of remote structures has primarily been derived from positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) studies. While metabolic and hemodynamic alterations are typical in these remote cortical areas after cortical infarct, there is no clear consensus regarding their role in functional recovery.

The motor cortex is composed of several cortical areas that are reciprocally interconnected (He et al. 1993; Stepniewska et al. 1993): the primary motor cortex (M1, area 4) located in the precentral gyrus; the premotor cortex [including ventral premotor cortex (PMV) and dorsal premotor cortex(PMD)], located anterior to M1; the supplementary motor area (SMA), located near the midline anterior to M1; and the cingulate motor areas, located in the cingulate gyrus on the medial surface of the cerebral cortex. It has been argued that each of these cortical motor areas plays a somewhat different role in the control of voluntary movements (Lawrence and Kuypers 1968; Luppino and Rizzolatti 2000). Since these cortical motor areas are interconnected, it is likely that the function of any one area will be affected by damage to one of the other areas. Furthermore, as premotor areas have efferent outputs to the spinal cord independent of M1, aspects of restitution of motor function may depend on the extent to which intact efferent systems can compensate or substitute for damaged motor areas (Strick 1988).

The theory that structures either adjacent or remote from the injured area can assume the function of the damaged cortex,
often referred to as vicariation of function or substitution (Munk 1881), has gained additional support due to recent examples of functional plasticity after injury. One study using microelectrode stimulation techniques showed that areas adjacent to damaged portions of motor cortex reorganize after behaviorally contingent electrical stimulation of the ventral tegmentum in rats (Castro-Alamancos et al. 1992). Another study using microelectrode-recording techniques showed that changes in functional representations in somatosensory cortex parallel sensorimotor skill recovery from stroke in adult monkeys, although it is unclear whether improvements reflect a recovery to normal preoperative strategies or the development of new compensatory behavioral strategies (Xerri et al. 1998). Subtle compensatory kinematic strategies have been documented during recovery of motor skill following a very small infarct in the M1 hand area of squirrel monkeys (Friel and Nudo 1998). That study suggests that the recovered behavior will rarely be identical to the preinjury behavior.

Previous studies in this laboratory have shown that following a focal vascular infarct in the M1 hand area of squirrel monkeys, the spared tissue adjacent to the injury undergoes alterations in functional topographic representations during the period of recovery (Nudo and Milliken 1996a; Nudo et al. 1996b). Spared hand representations in M1 are retained in animals that undergo motor skill training after the injury, while spared hand representations undergo further loss without training (i.e., during spontaneous recovery).

Numerous neuroimaging studies have suggested that plasticity occurs in remote motor areas after strokes affecting M1 in humans (Chollet et al. 1991; Cramer et al. 1997; see Cramer and Bastings 2000 for review). Metabolic and hemodynamic changes have been documented in premotor cortex (Weiller et al. 1992), SMA (Weiller et al. 1993), and M1 in the intact hemisphere (Cao et al. 1998; Nelles et al. 1999; Seitz et al. 1998). A recent study showed that 30-min induced inhibition of M1 results in increased recruitment curves in the contralateral M1 (Schambra et al. 2003). However, little is known about the detailed neurophysiologic changes in remote motor areas after vascular infarct in M1 that might accompany recovery. Studies in the somatosensory system indicate that damage to the primary somatosensory cortex (S1) results in topographic reorganization in the second somatosensory area (S2) (Pons et al. 1988). If this phenomenon is generalizable to the multiple motor cortical areas, then a general principle of compensatory response to brain injury may be postulated.

It was the goal of this study to examine potential reorganization in the hand representation of a secondary motor area, the ventral premotor cortex (PMV) following an experimentally induced ischemic infarct in the hand representation of M1. PMV was considered a good candidate for contributing to functional recovery after M1 injury due to its direct connections with M1 and its axonal projections to the spinal cord. Tracer injections of M1 in primates have revealed somatotopically distributed dense connections with PMV via intracortical axons (Stepniewska et al. 1993) PMV also contains neurons that project directly to the spinal cord; predominantly to the upper cervical segments (He et al. 1993; Nudo and Masterton 1990). Furthermore, microelectrode stimulation techniques have revealed low-threshold sites for elicitation of movement in PMV (Stepniewska et al. 1993). Recent evidence also suggests functional homology between premotor areas in monkey and human (Rizzolatti et al. 2002).

Using microelectrode stimulation techniques [(intracortical microstimulation (ICMS)), it is possible to elucidate the function of specific cortical motor areas by deriving high-resolution functional maps of topographic motor representations (Donoghue et al. 1992; Gould et al. 1986; Nudo et al. 1992, 1996a; Strick and Preston 1982). While most neurophysiologic studies of functional recovery from damage to M1 have concentrated on reorganization in the adjacent intact tissue (i.e., within M1), one would expect that reorganization in nonprimary motor representations, such as PMV, may also parallel functional recovery after M1 injury.

**METHODS**

ICMS techniques were used to derive detailed maps of M1 and PMV hand representations in five adult squirrel monkeys (*Saimiri sciureus*) before and after focal ischemic infarcts in the hand area of M1. First, hand preference and manual dexterity measurements were assessed for each animal using a pellet retrieval task that required skilled use of the hand. Then, ICMS mapping techniques were used to physiologically identify the M1 hand representation contralateral to the preferred hand, i.e., the target for the infarct. The PMV hand representation in the same hemisphere was also examined using the same stimulation techniques to obtain a baseline comparison to postinfarct maps. After derivation of the M1 and PMV hand area representations, a focal ischemic infarct of the electrophysiologically defined M1 hand area was induced. During a 3-mo recovery period, limited periodic assessment of hand preference and manual dexterity was conducted. However, no other repetitive training procedure, or any major intervention designed to encourage use of the more-affected limb, was employed. At the end of the 3-mo time period, a second set of representational maps of the M1 and PMV hand areas were derived in each animal.

**Behavioral methods**

To assess changes in hand preference and dexterity, random probe trials on an automated Klüver board were periodically conducted. This entailed presentations of flavored food pellets in wells of five different diameters, ranging from 9.5 to 25 mm, in random order. Normal retrieval of food pellets from the smallest well required the insertion of one or two fingers, as well as specific movement combinations (Nudo et al. 1996a). During probe trials for assessment of hand preference, a single 45-mg banana- or chocolate-flavored food pellet was placed randomly into one of the five wells, and the animal was allowed to retrieve it with either hand (i.e., open board probe trials). The mean percent of initial reaches with one hand plus the mean percent of retrievals with one hand (equally weighted) for all trials on an automated Klüver board trial. The mean percent of initial reaches with one hand plus the mean percent of retrievals with one hand (equally weighted) for all five wells was used to determine hand preference (Nudo et al. 1992). Five probe trials for each well size were conducted in each open board session. Additional random probe trials were periodically conducted using a restrictive barrier to isolate each hand and assess unimanual dexterity (a total of 25 trials for each hand; data from the hand ipsilateral to infarct are not presented here). Three sessions, conducted during the week prior to the preinfarct map (1 session every alternate day), were used to determine preinfarct hand preference and dexterity performance. Sessions consisting of probe trials (both open-board and hand-restricted) were continued during the postinfarct period to track recovery. During the first 4 weeks, three sessions were conducted each week; during the final 8 weeks, one session was conducted each week. Videotapes of individual trials were analyzed to determine the total number of finger flexions per retrieval and then averaged for each day. These values were normalized relative to preinfarct flexions per retrieval. As a second measurement of postinfarct performance, the
same videotapes were further analyzed to determine the amount of time that the digits were within each well before a successful retrieval (well time). These values were then normalized relative to the average preinfarct well times. These data were later analyzed using the Dunnett test for pairwise mean comparisons to examine differences between baseline (preinfarct) performance and each weekly mean performance (Keppel 1982).

**Surgical and electrophysiological procedures**

Details of surgical and electrophysiological procedures have been presented previously (Nudo et al. 1996a). Briefly, all surgical procedures were conducted under aseptic conditions. Under halothane/nitrous oxide gas anesthesia, a craniotomy was performed over the M1 and PMV hand representations. A cylinder was affixed over the opening and filled with warm, sterile silicone oil. Gas anesthesia was then withdrawn, and ketamine was administered. Throughout the experimental procedure, core temperature and vital signs were monitored, and intravenous fluids were given. ICMS mapping procedures were then conducted under ketamine anesthesia. Care was taken to maintain a relatively stable anesthetic state. A glass micropipette filled with 3.5 M NaCl (impedance, ~600 kΩ) was advanced perpendicular to the cortex to a depth of approximately 1750 μm (layer 5). The stimulus consisted of thirteen 200-μs cathodal pulses delivered at 350 Hz and repeated at 1/s. Interpenetration distances of 250 and 500 μm were used in the PMV and M1 hand areas, respectively. Movements evoked by ICMS at near-threshold levels defined movement fields (maximum current, 30 μA). From these neurophysiologic data, representational map boundaries were determined to outline different cortical efferent zones. Each zone contained microelectrode penetration sites at which stimulation evoked a specific movement. Further details of these procedures and discussion of possible sources of variation in ICMS-derived motor maps are found elsewhere (Friel and Nudo 1998; Nudo et al. 1992, 1996a).

**Map construction and areal measurements**

Representational maps of response zones were generated by a computer algorithm that used the x-y location of electrode penetrations to establish unbiased borders midway between adjacent sites with different response representations. The hand representation was defined as cortical regions in which ICMS evoked movement of the distal forelimb at near-threshold current levels. These movements include finger, thumb, wrist, and forearm (sensation and pronation) movements, but exclude elbow and shoulder movements. Due to necrosis and scavenging of the infarcted tissue, histological examination, although useful for verifying that all layers of the infarcted area were destroyed, could not be used to accurately define the volume of the lesion. A less direct method was therefore used to measure the areal extent of the M1 infarct. This method takes advantage of the fact that after vascular electrocoagulation, the ischemic cortex becomes blanched and easily distinguished from noninfarced tissue. Therefore the postinfarct estimate of intact M1 hand area was derived by superimposing a digital photograph of the postinfarct intact vasculature on the preinfarct photograph 3 mo after the ischemic lesion (Friel and Nudo 1998). Using this estimation technique, the areal extent of the M1 surface destroyed by the infarct and the cortical area spared by the infarct was determined. Data obtained via visual inspection was verified using a laser-Doppler blood flow imaging device (Moor Instruments) (Fig. 1) 1 h after the ischemic infarct to determine the precise area of reduced blood flow. The results of the Doppler blood flow imaging was coincident with the infarct area defined by visual inspection. Comparing the two approaches, boundaries differed by <100 microns, well within the range of our ability to resolve the precise boundary using either technique. PMV hand area measurements were taken from the ICMS maps of PMV before and after the ischemic infarct. Measurement differences were then compared using Fishers LSD Post Hoc analysis (Keppel 1982).

**Infarct procedure**

After derivation of the baseline M1 and PMV hand representation areas contralateral to the preferred hand, blood vessels supplying the M1 hand representation area were permanently occluded as they entered the cortical surface by using microforceps connected to a bipolar electrocoagulator. This model was not designed to mimic clinical stroke per se, but to provide a reliable method for producing physiologically identified ischemic infarcts. This technique consistently produced focal, columnar infarcts through all six layers of the cerebral cortex. In both this and in previous studies, the infarcts were predictable in size and did not affect the underlying white matter (Nudo and Milliken 1996; Nudo et al. 1996b). At the conclusion of each procedure, gas anesthesia was reintroduced for surgical closing. The animal was then monitored in a temperature-controlled incubator until it was awake and alert. Animals were cared for in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and with the approval of the Institutional Animal Care and Use Committee. After completion of these experiments, each monkey was given a lethal dose of sodium pentobarbital (100 mg per kg of body weight) and perfused transcardially for histological examination of each lesion.

**RESULTS**

**Behavioral results of infarct in M1**

The infarct initially resulted in a marked deficit in the ability to retrieve food pellets with the hand contralateral to the lesion, especially from the smallest wells. In the first 3 days, there was little voluntary use of the affected limb for either food manipulation or movement about the home cage. The elbow of the affected limb was usually held in an extended position, and only reflexive grasping with the affected hand was observed. In
the following 7 days, voluntary use of the affected hand gradually returned, although monkeys still had difficulty placing fingers into the smallest wells and were unable to retrieve pellets from the smallest wells with the impaired hand.

By the end of the second week after the infarct, the monkeys were able to retrieve pellets from the smallest well, but manual skill, as measured by the total number of finger flexions per pellet retrieval, was markedly diminished and highly variable across trials. More specifically, the average number of flexions per retrieval from the smallest well in the second week after infarct was 2.5 times that observed in the week before the infarct. This initial postinfarct motor impairment of the contralateral hand was followed by a gradual improvement in performance over 1–3 months. The average flexions per retrieval in week 12 after infarct was reduced to 1.6 times that in the week before infarct, demonstrating some spontaneous recovery, but a lasting residual deficit (Fig. 2A; data from the smallest well, well 5, shown). Motor performance indices were not statistically different from baseline values at any week postinfarct despite elevated postinfarct mean values. This is likely due to the relatively small number of monkeys in the study, because some values approached statistical significance.

Although the monkeys were able to retrieve pellets from the smallest well by the end of the second week postinfarct, the amount of time spent in the well for each retrieval was greater than the time spent preinfarct, although the well time was highly variable across animals (Fig. 2B). Average well time per retrieval was 5.5 times greater at the end of the second week compared with preinfarct baseline ($P < 0.05$). Well time performance improved in postinfarct week 3, but did not fully return to preinfarct performance levels by week 12. In comparing the flexions per retrieval (motor performance index) and

![Graph A](image)

**Fig. 2.** Effects of ischemic infarct on motor performance and hand preference. **A:** normalized well 5 (smallest well) motor performance of the impaired hand for 4 monkeys in weekly epochs. Evaluation of motor performance was conducted using a Plexiglas barrier that required the monkey to use the impaired hand only. The motor performance index is the number of finger flexions per retrieval divided by the baseline (preinfarct) flexions per retrieval for each animal from the smallest well. Bars represent the mean normalized flexions per retrieval (±SE). One animal (0003) is not included due to insufficient preinfarct data. **B:** normalized well 5 time performance of the impaired hand for the same 4 monkeys. Normalized well time is the amount of time the hand is in the well before a successful retrieval divided by the baseline (preinfarct) well time per retrieval. Bars represent the mean normalized well time per retrieval (±SE). Well time performance for pellet retrieval increased immediately postinfarct ($P < 0.05$), followed by an improvement in performance in postinfarct week 3. Well time performance did not return to preinfarct performance levels through week 12. C: percent successfully retrieved pellets from the smallest well was significantly decreased in postinfarct week 1 ($*P < 0.01$) compared with preinfarct percentage. **D:** percent use of the initially preferred hand for 4 monkeys in weekly epochs. Assessment of hand preference was conducted using an open Kluver board. Bars represent the mean percent use of the preinfarct preferred hand (±SE). The animal with the smallest M1 lesion (9902) did not change hand preference and is not included. Each postinfarct epoch mean differs significantly from the preinfarct mean ($*P < 0.01$).
well time performance across the postinfarct period, the higher mean index values of well time suggest that well time may be a more sensitive measure of motor performance on this task. The percentage of successfully retrieved pellets from the smallest well was significantly decreased in postinfarct week 1 ($P < 0.01$) and week 2 ($P < 0.05$) and gradually returned to the preinfarct level of 100% in each animal (Fig. 2C).

Postinfarct hand preference changed to the less-affected hand in the four monkeys with the largest infarcts (based on the percentage of the M1 hand area infarcted). The monkey with the smallest injury to M1 did not change hand preference. In those animals with the largest infarcts, the average use of the initially preferred hand significantly decreased from 74.3 ± 14.8% (SE) in the week before infarct to 4.3 ± 4.8% in the second week after infarct ($P < 0.01$). This change in hand preference was still evident at 12 weeks postinfarct, when the percent use of the initially preferred hand was 30.7 ± 16.6% ($P < 0.01$; Fig. 2D).

Postinfarct impairment in performance was also evident in the larger wells (1–4), with each animal showing an increase in motor performance index postinfarct, with a gradual improvement in performance thereafter (Fig. 3). The mean motor performance index for well 3 was significantly higher in week 2 postinfarct ($P < 0.01$) and remained higher than preinfarct performance throughout the 12-wk postinfarct testing period. Performance on well 4 was significantly higher in weeks 2 and 3 postinfarct ($P < 0.05$) and remained higher throughout the 12-wk testing period.

**Functional reorganization in ventral premotor cortex**

Comparison of ICMS maps of movement representations in PMV before and 12 wk after the infarct revealed substantial enlargement of the hand representation in the PMV cortex ipsilateral to the experimentally induced infarct (Figs. 4 and 5). ICMS mapping and histological examination of M1 12 wk after the ischemic lesion revealed a decrease in the M1 hand area in all five animals. Partial survival of cortical tissue in the M1 hand area was seen in each monkey. The absolute size of the infarcted M1 area ranged from 6.0 to 16.6 mm$^2$ (Fig. 6). This variation was, in part, due to the variation in size of the preinfarct hand area in individual monkeys. However, the relative size of the infarcted area also varied. Individual percentages of the original M1 hand area that was infarcted ranged from 57 to 96.5%, with a mean loss of 81.3 ± 15.8% (Fig. 7).

ICMS mapping of the PMV hand area at 3 mo postinfarct revealed a net expansion in the PMV hand representation in each monkey, ranging from 0.3 mm$^2$ (i.e., from 3.9 to 4.2 mm$^2$)
FIG. 4. Reorganization of hand representations in the ventral premotor cortex before and after a focal ischemic infarct in the hand representation of primary motor cortex. Left: schematic representation of the forebrain of the squirrel monkey from a lateral view showing the location of the M1 distal forelimb area (df1) and the location of ventral premotor cortex (PMV). Right: results of ICMS mapping of the PMV hand area in 1 monkey (9406) before (top) and 12 wk after ischemic infarct in the M1 hand area (bottom). Circles represent the location of microelectrode penetrations and colors represent the movement(s) evoked by near-threshold electrical stimulation (<30 μA) at that site. In this animal (9406), the infarct damaged 79% of the preinfarct M1 hand representation area and postinfarct PMV mapping revealed a 45% increase in the PMV hand representation. In each animal, an increase in the area of distal forelimb movement representation occurred 12 wk after infarct in M1. Scale bar = 1 mm.

FIG. 5. The results of ICMS mapping of the PMV hand area before and 3 mo after the ischemic infarct in 4 monkeys. ICMS mapping revealed a net expansion in the PMV hand representation in each monkey. Different colors represent the evoked movement(s) of particular body parts at near threshold levels at each penetration site. Scale bars = 1 mm.
to 1.9 mm$^2$ (i.e., from 3.5 to 5.4 mm$^2$; Fig. 6). These increases
ranged from 7.2 to 53.8% relative to the initial PMV hand area,
with a mean increase of 36.0 ± 20.8% ($P < 0.05$; Fig. 7). The
variation in the sizes of the infarcts in M1 allowed us to
examine the relationship between infarct size and degree of
reorganization in PMV. This analysis revealed that the increase
in the PMV hand representational area was directly propor-
tional to the relative size of the M1 infarct ($R^2 = 0.819$; $P =
0.0348$). The animal that had the smallest infarct in the M1
hand area (also the animal that did not change hand preference
after infarct), had the smallest expansion in the PMV hand area
representation. The expansion of the PMV distal forelimb
representation does not appear to be linked to the size of the
initial M1 hand area, since the two animals with the largest
initial hand areas, 9902 and 0004, had relatively small and
large PMV changes, respectively (Figs. 6 and 7). When the
PMV hand representation was subdivided into digit and wrist-
forearm representations, the digit area increased in four mon-
keys and decreased in one monkey (−7.1, 15.0, 20.8, 97.1, and
44.0%: in the same order as the individual animal data pre-
sented in Figs. 6 and 7), with a mean change of +34.0% (not
significant, $P > 0.05$). The wrist-forearm area increased in four
monkeys and decreased in one monkey (14.2, −35.8, 245.9,
40.0, and 50.2%) with a mean change of +62.9% (not signif-
icient, $P > 0.05$; also in the same order as the individual animal
data presented in Figs. 6 and 7). Combination digit and wrist
areas were included in both digit as well as wrist areas.

Current thresholds for stimulation of evoked movements
were not different from those observed in M1 and were quite
low. This may suggest that direct corticospinal connections
mediate the movements evoked from stimulation of PMV.
Furthermore, stimulation thresholds in PMV did not change
postinfarct, suggesting that movements were not mediated
transcortically via M1. EMG recordings were not conducted
during the mapping procedures, so latencies of EMG responses
could not be analyzed.

**DISCUSSION**

The changes found in the hand movement representation in
PMV following ischemic infarct in the hand representation of
M1 indicate that neurophysiologic reorganization of more re-
omeote cortical motor areas occurs in response to cortical infarct
in M1. Further, since analogous results have been observed in
the somatosensory cortex (Pons et al. 1988), it would appear
that reorganization of secondary cortical areas is a general
feature of injury-induced plasticity. Still further, because the
degree of functional expansion in PMV is directly proportional
to the amount of damage in M1, a second general principle is
suggested. That is, remote reorganization is directly related to
the reciprocal connectivity of the various motor areas. The
greater the damage to reciprocal intracortical pathways, the
greater the plasticity in the secondary, intact area.

Evidence for the contribution of premotor cortex to recovery
has come from both human (Fridman et al. 2002; Miyai et al.
1999) and animal (Castro-Alamancos and Borrel 1995; Liu and
Rouiller 1999) studies. Neuroimaging studies have reported
altered metabolic and hemodynamic changes in premotor cor-
tex after cortical injury in humans (Weiller et al. 1992). Results
from a recent transcranial magnetic stimulation study suggest
that premotor cortex contributes to functional motor recovery
in human stroke patients (Fridman et al. 2002). Miyai et al.
(1999) reported that following middle cerebral artery occlu-
sion, recovery in human stroke survivors was improved in those
with intact premotor cortex compared with those that had
premotor cortex damage. Following damage to M1 and subse-
quent spontaneous recovery of upper extremity functions in
macaque monkeys, Liu and Rouiller (1999) showed that initial

**FIG. 6.** The results of ICMS mapping of the M1 and PMV
hand areas before and 5 mo after the ischemic infarct. Left: M1
hand area. The results revealed decreases in the M1 hand area
in all 5 animals. Although the entire hand area was targeted for
infarct, partial retention of spared hand area was seen in all 5.
The decrease in absolute M1 hand area ranged from 6.0 mm$^2$
in 1 animal (9406), to 16.6 mm$^2$ in another (0004). Right:
PMV hand area. There was an increase in the total area of the
hand representation in PMV at 3 mo postinfarct in all 5
animals. This increase ranged from 0.3 (9902) to 1.9 mm$^2$
(0003).

**FIG. 7.** Relative change in hand area in M1 and PMV 12 wk
postinfarct. Left: percent change in hand area in M1 and PMV
3 mo postinfarct in 5 animals. The percent of M1 hand area lost
ranged from 57.0% (9902) to 96.5% (0003), with a mean of
81.3 ± 15.8%. The percent increase in PMV hand response
area ranged from 7.2% (9902) to 53.8% (0004), with a mean of
36.0 ± 20.8%. Right: percent increases in PMV hand response
area as a function of the percent anatomical loss of M1 hand
area 3 mo postinfarct. All 5 animals had an increase in the area
of the hand response representation in PMV that was propor-
tional to the amount of M1 hand area lost. In general, the larger
the infarct area and greater the percentage of M1 hand response
area lost, the larger the increase in the PMV hand response area
($R^2 = 0.819$; $P = 0.0348$).
behavioral deficits were reinstated when PMV and dorsal premotor cortex were pharmacologically inhibited. Other studies have implicated PMV in various aspects of motor planning, execution, and learning in normal human (Winston et al. 1997) and nonhuman (Kurata and Hoshi 1999) primates. These results suggest that reorganization in PMV and other nonprimary motor areas may provide a neural substrate for adaptive motor behavior and contribute to postinjury recovery of upper extremity motor functions such as manual dexterity.

Many of the cellular and synaptic substrates that support adaptive plasticity in the adult cortex are now well established. Motor learning, or the development of more complex motor behaviors, has been shown to result in both anatomical and physiological changes within sensorimotor cortex. A greater number of synapses per neuron, an increase in dendritic arborizations, and strengthened or enhanced synaptic responses have each been demonstrated following skilled motor learning or exposure to complex environments (Greenough et al. 1985; Jones et al. 1997; Kleim et al. 1996; see Nudo et al. 2001 for review). Similar anatomical changes have been seen in intact contralateral cortex with skilled use training following cortical injury (Kleim et al. 1996; Jones and Schallert 1994; Jones et al. 1999). Motor skill training using a small-object retrieval task has been shown to alter the functional organization of primary motor cortex via an expansion of distal forelimb representations in both rats (Kleim et al. 1998) and primates (Friel and Nudo 1998; Plautz et al. 2000). It seems reasonable to conclude that similar anatomical and physiological changes may occur in connected nonprimary motor and sensory areas in both normal and cortically injured animals.

Several studies have shown that reductions in GABA<sub>A</sub> receptor density and a concurrent increase in glutamate N-methyl-D-aspartate (NMDA) receptor density occurs in multiple brain areas connectionally related to damaged areas of cortex after infarcts in rodents (Qu et al. 1998a,b; Redecker et al. 2000; Scheine et al. 1996). These changes may act to unmask latent horizontal connections that could contribute to map alterations (Jacobs and Donoghue 1991).

It is now clear that intact motor cortical areas, including those in remote areas interconnected with the damaged motor area, undergo substantial anatomical and neurochemical changes that may contribute to recovery of lost function. The proportional relationship between relative size of the cortical injury and the remote cortical reorganization demonstrated in the present study suggests that post-stroke cortical plasticity is driven by reciprocal intracortical connections between the damaged and intact areas. A direct link between reorganization of PMV and behavioral recovery could not be established in this study due to the variation in M1 lesion size and its relationship with the change in PMV hand area. Future studies should address this issue more directly. In addition to producing similar infarcts with respect to size and location, it will be necessary to determine the correlation (if any) between PMV map expansion and the degree of behavioral recovery. These studies will require similar infarct sizes and a battery of behavioral assessments. Further experiments testing the behavioral consequences of PMV disruption in activity after M1 infarct may also allow for a more direct link between PMV reorganization and motor recovery after M1 injury.

Unlike macaque monkeys, there have been no delineations of sub-areas within PMV in New World monkeys. Studies in owl monkeys have demonstrated a low-threshold hand representation in PMV with stimulation at many sites that evoke movements of multiple joints (Gould et al. 1986; Stepniewska et al. 1993). Large numbers of corticospinal neurons have been found in every primate species studied to date that correspond to the PMV hand area (“Region C” in Nudo et al. 1995; see also Dum and Strick 1991). While it has been reported that the density of corticospinal neurons in macaques approaches that in M1 (Dum and Strick 1991), a comparative study later reported that the density of corticospinal neurons in PMV of squirrel monkeys is higher than in macaques (Nudo et al. 1995). Kakei et al. (2001) showed that most neurons in PMV are extrinsically and directionally tuned regardless of large changes in forearm posture, suggesting that PMV is involved in the spatial guidance of limb movements. PMV may be involved in the transformation of target location in a visual frame of reference into the direction of motor action to acquire the target via its connections with M1. This area, presumed to be F4, appears to code goal-directed actions mediated by spatial locations (Rizzolatti et al. 2002). F5 has been shown in macaques to be involved in motor-action recognition (Umiltà et al. 2001) as well as in hand shaping in visuomotor transformations for grasping and manipulation (Fogassi et al. 2001). Human area 44, believed to be homologous to F5 in macaques (Rizzolatti et al. 2002), has been shown to be involved in sensorimotor transformations for grasping and manipulation (Binkofiski et al. 1999). Until further behavioral, neurophysiological, and anatomical studies are conducted, it is not yet possible to designate any particular region of squirrel monkey PMV as F4 or F5.

It is feasible that nonprimary motor areas such as PMV contribute to functional recovery following injury in M1. Along these lines, it is important to note that increases in the PMV hand representation reported here occurred in spontaneously recovering animals. In marked contrast, in spontaneously recovering animals after more limited M1 infarcts, the hand representation in the intact, adjacent M1 tissue decreased substantially. It is now of great interest to understand the modulatory effects of behavioral interventions (i.e., physiotherapy) on neurophysiologic reorganization in premotor cortex, such as has been demonstrated for peri-infarct M1 regions (Liepert et al. 2000; Nudo and Mil liken 1996; Nudo et al. 1996b). The plastic changes observed here may perhaps be magnified in PMV and other remote areas with appropriate physiotherapeutic and/or pharmacotherapeutic interventions.

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