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Effects of Small Ischemic Lesions in the Primary Motor Cortex on Neurophysiological Organization in Ventral Premotor Cortex

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Dancause, Numa, Scott Barbay, Shawn B. Frost, Elena V. Zoubina, Erik J. Plautz, Jonathan D. Mahnken, and Randolph J. Nudo. Effects of small ischemic lesions in the primary motor cortex on neurophysiological organization in ventral premotor cortex. *J Neurophysiol* 96: 3506–3511, 2006. First published September 20, 2006; doi:10.1152/jn.00792.2006. After a cortical lesion, cortical areas distant from the site of injury are known to undergo physiological and anatomical changes. However, the mechanisms through which reorganization of distant cortical areas is initiated are poorly understood. In a previous publication, we showed that the ventral premotor cortex (PMv) undergoes physiological reorganization after a lesion destroying the majority of the primary motor cortex (M1) distal forelimb representation (DFL). After large lesions destroying >50% of the M1 DFL, the PMv DFL invariably increased in size, and the amount of the increase was positively correlated with the size of lesion. To determine whether lesions destroying <50% of the M1 DFL followed a similar trajectory, we documented PMv reorganization using intracortical microstimulation techniques after small, ischemic lesions targeting subregions within the M1 DFL. In contrast to earlier results, lesions resulted in a reduction of the PMv DFL regardless of their location. Further, because recent anatomical findings suggest a segregation of PMv connectivity with M1, we examined two lesion characteristics that may drive alterations in PMv physiological reorganization: location of the lesion with respect to PMv connectivity and relative size of the lesion. The results suggest that after a lesion in the M1 DFL, the induction of representational plasticity in PMv, as evaluated using intracortical microstimulation, is related more to the size of the lesion than to the disruption of its intracortical connections.

INTRODUCTION

After injury to the primary motor cortex (M1), the physiological and anatomical organization of premotor areas is altered. Because spared cortical structures may play a role in recovery (Liu and Rouiller 1999; Miyai et al. 1999), it is of clinical and theoretical interest to better understand the factors driving plasticity in remote structures. When infarcts destroyed the majority of the distal forelimb representation (DFL) of M1 (57–97%), we observed an increase in the size of the PMv DFL (Frost et al. 2003).

Although it is not yet clear what drives the adaptive changes in PMv, it has been suggested that when a functional area is completely destroyed, other distant cortical area(s) can vicariously take over the function that was lost after the lesion (Glees and Cole 1950). However, after small lesions, the surviving cortex within a given functional area might be able to generate the behaviors previously controlled by the entire area (Lashley 1929, 1930). To test the physiological correlate of this hypothesis, we performed small, selective lesions in the M1 DFL and determine if lesions destroying <50% of the M1 DFL would result in changes in PMv functional organization. Such lesions are known to result in distinctive, but transient deficits in skilled hand use (Friel et al. 2005).

METHODS

Four adult, experimentally naïve squirrel monkeys (Genus *Saimiri*) were used in the present experiments. All animal use was in accordance with a protocol approved by the Institutional Animal Care and Use Committee of the University of Kansas Medical Center.

Behavioral assessments

Two weeks prior to the first surgical procedure, hand preference on a reach and retrieval task was evaluated using techniques described in detail in previous publications (Nudo et al. 1992). The same retrieval task was used for motor skills assessment. Initial training and documentation of pre- and postlesion behavior was identical to that described in a report of the effects of larger M1 lesions (Frost et al. 2003).

Electrophysiological identification of M1 and PMv distal forelimb representations

Intracortical microstimulation (ICMS) mapping techniques were used to define the distal forelimb and adjacent proximal representations in M1 and PMv (Frost et al. 2003). After a craniotomy, a 3.5M NaCl-filled glass microelectrode was used for electrical stimulation applied at a depth of ~1,750 μm. Stimulation consisted of a 40-ms train of 13 monophasic cathodal pulses of 200 μs delivered at 350 Hz from an electrically isolated, constant current stimulator (Nudo and Milliken 1996; Nudo et al. 1992). Pulse trains were repeated at 1-Hz intervals; current was ≤30 μA. Microelectrode interpenetration distances in PMv were ~250 μm and ~500 μm in M1. We included in the DFL all sites at which electrical stimulation elicited movements of the digits, wrist, or forearm (Fig. 1). Twelve weeks after the ischemic lesion, a second mapping procedure was performed to document the physiological reorganization of M1 and PMv. For further details of these procedures and a discussion of the possible sources of variation

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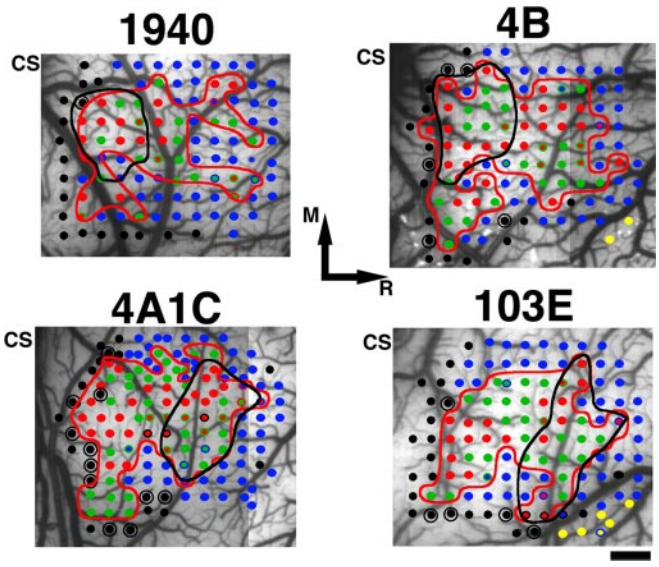

FIG. 1. Lesion locations in relation to intracortical microstimulation (ICMS) movement maps in primary motor cortex (M1). Location of intended lesion (black contour) in relation to ICMS-evoked movements within M1. Digit and wrist/forearm movement were considered to be a part of the distal forelimb representation (DFL), indicated with a red contour. Each dot represents a microelectrode penetration site. For sites where multi-joint responses could be evoked, the color in the center of the dot depicts the movements evoked at the lowest threshold and the outer ring show movement evoked by increasing the stimulation current ≤ 2 μA. Some nonresponsive sites (i.e., no movement evoked at 30 μA) were verified at different time points during the ICMS procedures (large black rings). Black dots, nonresponsive; blue, proximal movements; green, wrist/forearm; red, digit; yellow, orofacial; CS, central sulcus; Scale bar = 1 mm.

in ICMS-defined motor maps, see Donoghue et al. 1992; Nudo et al. 1992, 1996b; Strick and Preston 1982.

Cortical infarct methods

Electrocoagulation techniques were used to occlude the blood vessels supplying a delimited portion of the M1 DFL (see following text) by passing electrical current between the tips of microforceps connected to a bipolar electrocoagulator. The resulting lesions using this technique consistently correspond to the intended infarct zone and extend through all layers of cortical gray matter without directly affecting the underlying white matter (Nudo and Milliken 1996; Nudo et al. 2003). Lesions in two of the four cases were targeted in the caudomedial portion of the M1 DFL ($M1_{cm}$), whereas two were targeted in the rostrolateral portion of the M1 DFL ($M1_{rl}$) (Dancause et al. 2006). The extent of each electrocoagulation lesion was verified by laser Doppler blood flow imaging (Moor Instruments) at 1 h postinfarct, the region of ICMS-defined motor responses elicited 12 wk after the lesion, and the histologically defined necrosis in the postmortem tissue (~5 mo after the lesion). All three techniques showed close correspondence for the limits of the infarcted zone. The size of the M1 infarct was measured in each case and expressed as a proportion of the total M1 DFL.

Analysis of neurophysiological reorganization

A custom-designed computer program was used to unambiguously circumscribe sites the stimulation of which evoked movements of the same category (e.g., digit, wrist, etc.) (Nudo et al. 1992). The cortical surface areas occupied by each movement category in the representational maps were then color-coded and analyzed using an image analysis program (Scion IMAGE, version 1.63). Finally, areas were compared in maps derived before and 12 wk after the lesion.

RESULTS

Localization of M1 and PMv distal forelimb representations

The M1 DFL was found immediately rostral to the central sulcus (Nudo et al. 1992; Strick and Preston 1982). Based on ICMS results, the caudal border of the DFL was defined by unresponsive sites corresponding to area 3a, whereas the medial, lateral, and rostral borders were defined by evoked movements of proximal joints. The PMv DFL was located rostral and lateral (ventral) to the M1 DFL (Frost et al. 2003). The DFLs of M1 and PMv were typically separated by proximal (movements evoked at the shoulder and elbow joints and occasional trunk movements) and orofacial representations. The PMv DFL was bordered by orofacial representations caudally. Other borders generally consisted of proximal representations.

Topographic details of lesions in M1

The specific location of the intended lesion in each case is shown in Fig. 1*A*. Twelve weeks after the injury, it was determined that the ischemic lesion in M1 destroyed between 29 and 41% of the total DFL based on initial laser Doppler blood flow images and confirmed by necrosis (Frost et al. 2003). The average lesion size was 4.97 $\pm$ 1.01 (SD) mm^2.

After the lesion, all animals showed mild behavioral deficits on the reach and retrieval task using the impaired forelimb (contralateral to the ischemic infarct). In the first week postinfarct, animals typically used the less impaired forelimb to retrieve pellets. When the more impaired forelimb was used, retrieval generally required more digit flexions per retrieval and/or the time necessary to retrieve the pellets was increased. As described in Friel and collaborators (2005), after $M1_{rl}$ lesions, monkeys often fail to direct the hand accurately to the well. There is an increase of contacts to the surface of the board outside the well before entering the well. In contrast, after $M1_{cm}$ lesions, monkeys frequently examine their palm visually for the presence of the pellet after an attempted retrieval as if they cannot feel the pellet in their hand. Over the course of the following 3 wk, behavioral performance returned to prelesion levels.

Physiological reorganization in PMv after small ischemic lesions in M1

Twelve weeks after the ischemic lesions, postinfarct ICMS-motor maps were derived. The PMv DFL was reduced in each of the four monkeys (mean area loss = 0.57 $\pm$ 0.48 mm^2; mean percentage loss = 14.9 $\pm$ 11.7% of prelesion area; Fig. 2). A paired Student's *t*-test demonstrated a significant effect of the lesion on the PMv DFL ($t = 3.06$; $P \leq 0.05$) but no other more specific movement category.

Factors determining neurophysiological reorganization in PMv

Taken together with previous results (Frost et al., 2003), it appears that large lesions (>50% of the M1 DFL) generate significant expansions in PMv DFL, whereas small lesions

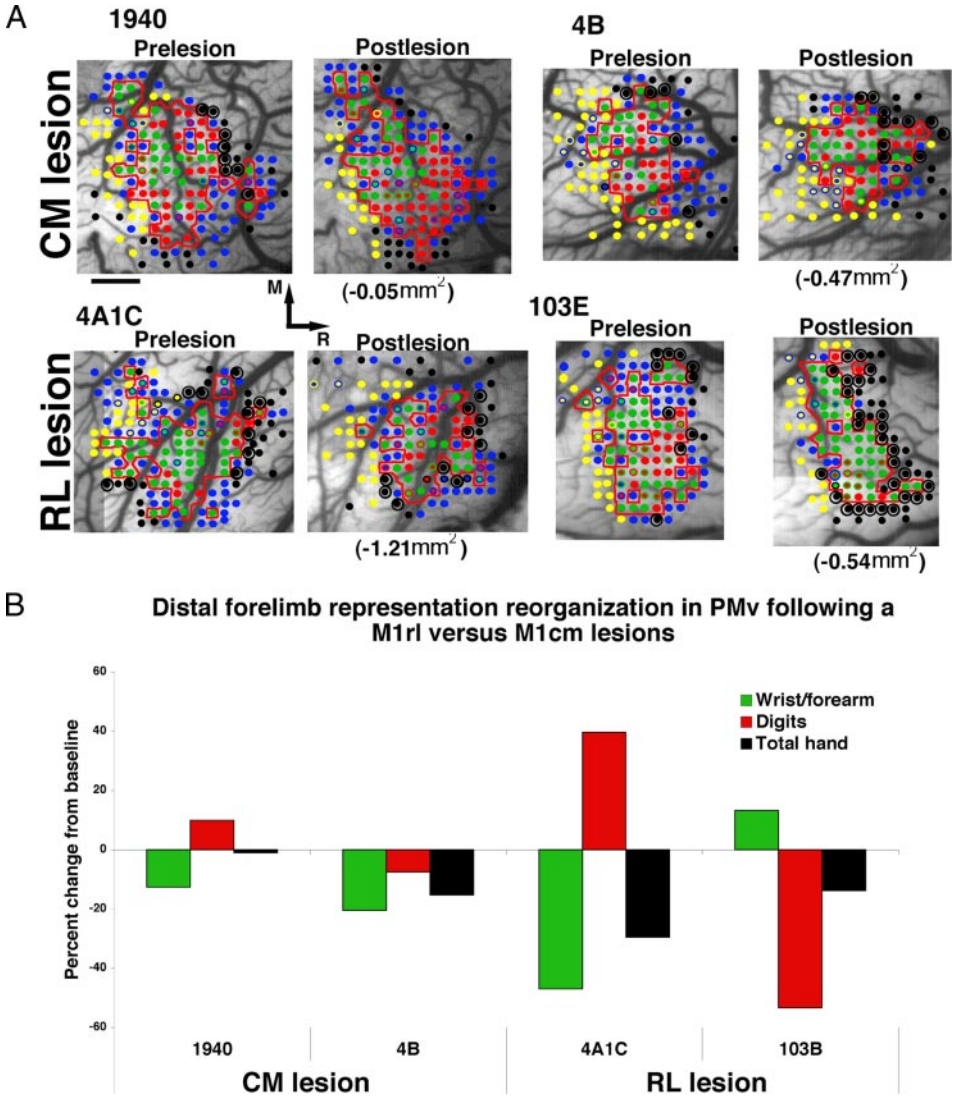

FIG. 2. Reorganization of ICMS maps in ventral premotor cortex (PMv) 12 wk after M1 lesions. *A*: for each case, ICMS map of PMv DFL (black contour) is shown prior to, and 12 wk after the ischemic lesions in M1. *Top*: 2 cases with the $M1_{cm}$ lesions; *bottom*: 2 cases with the $M1_{rl}$ lesions. *B*: analysis of the changes in PMv DFL was achieved using a custom-made analysis program (see METHODS). The total DFL in PMv was reduced in each of the 4 cases. A change in PMv DFL reported as a percentage of prelesion area.

(<50% of the M1 DFL) generate significant reductions in PMv DFL. However, this simple size relationship may be confounded by the heterogeneous distribution of connections between PMv and M1. In squirrel monkeys, PMv projects primarily to the $M1_{rl}$ and only sparsely to $M1_{cm}$ (Dancause et al. 2006). Because lesions in the present four cases, and those reported in the earlier study by Frost and collaborators (2003) were distributed throughout various portions of the M1 DFL, it was possible to estimate the relative contribution of lesion size and location on PMv reorganization.

To estimate the proportion of M1-PMv connections disrupted by each of the lesions, we used previous anatomical data on the connectivity of M1 and PMv DFLs collected from control (noninfarcted) squirrel monkeys (Dancause et al. 2005). Because of the consistency in the labeling patterns across individuals, we used a single case, with the largest injection in PMv, to represent the distribution of PMv terminal labeling across the expanse of the M1 DFL (Fig. 3*A*). The representative case then was warped to a common, idealized rectangular space (MorphX v2.9; Fig. 3*B*). Next, each of the four M1 DFL maps and ischemic infarcts in the present experimental series, as well as five cases in the earlier series (Frost et al. 2003), were warped to the idealized rectangular space. The superposition of warped experimental maps to the control map allowed approximation of the lesion effect (Fig. 3*C*). The estimated number of terminals and cell bodies contained within each lesion was tallied and expressed as a proportion of total terminals or cell bodies within the M1 DFL. In the present report, because of the reciprocity of connections between PMv and M1, the proportion of "connections" is defined simply as the average of the proportion of terminals and the proportion of cell bodies within each subregion [i.e., (% terminals + % cell bodies) ÷ 2].

As expected, the proportion of PMv-M1 DFL connections theoretically disrupted by $M1_{rl}$ lesions (71.7 ± 0.71%) was far greater than the proportion disrupted by $M1_{cm}$ lesions (6.2 ± 3.0%). Combining these four small lesion cases with the five larger lesions from the previous study, a linear regression analysis found no clear relationship between the degree of disruption of M1-PMv connectivity and the postinfarct alterations in the PMv DFL (Fig. 4*A*; $R^2 = 0.3018$ $P = 0.1255$). In contrast, a linear regression analysis demonstrated that over 87% of the variance in the plasticity of the PMv DFL could be explained by the proportion of the M1 DFL destroyed by the lesion ($R^2 = 0.87$; $P = 0.0002$; Fig. 4*B*). The reversal between increase and decrease of PMv DFL occurred at lesion sizes that

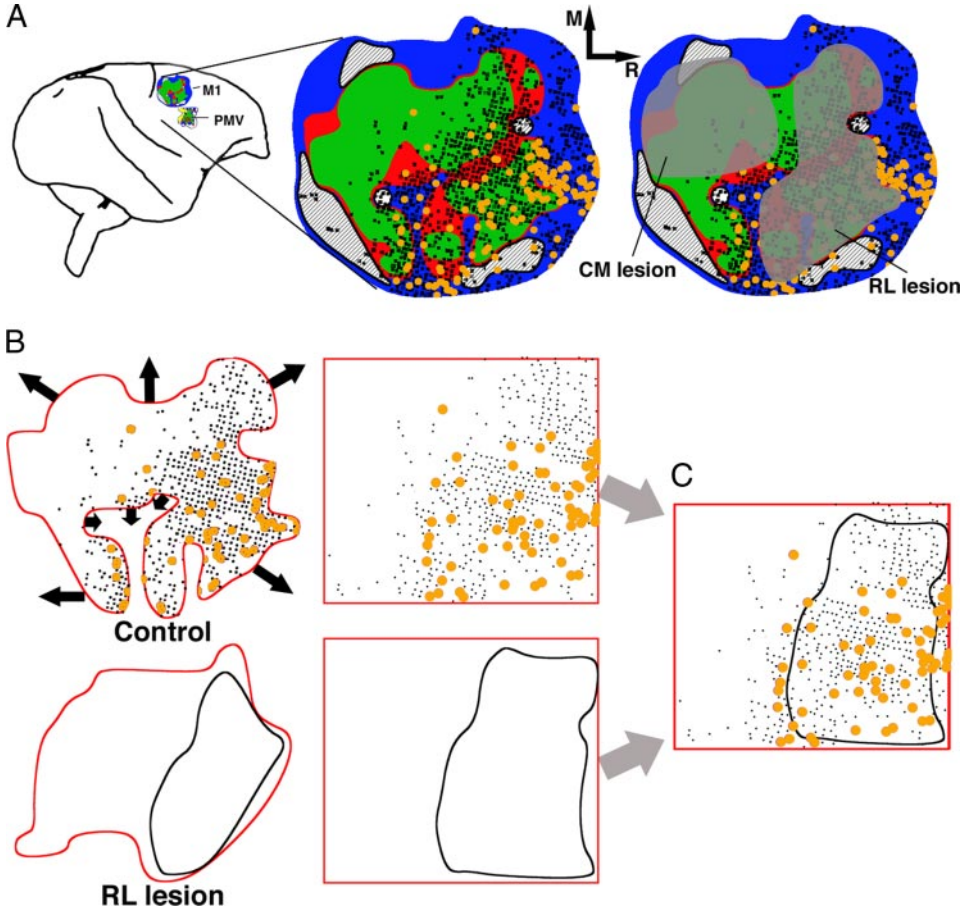

FIG. 3. Location of $M1_{rl}$ and $M1_{cm}$ lesions in relation to PMv-M1 connectivity. *A*: cartoon of a squirrel monkey brain showing the approximate location of the M1 and PMv DFL. The typical distribution of labeled cell bodies (large orange dots) and terminals (small black dots) in M1 DFL after injection of biotinylated dextran amine (BDA) in PMv in a control case (large injection; *cases 1934*) (Dancause et al. 2005) are shown. Based on these data, $M1_{rl}$ lesions destroy the majority of PMv connections with M1 DFL, whereas $M1_{cm}$ lesions have minor impact. Digit representations, red; wrist/forearm, green; proximal, blue; nonresponsive, hatched black. *B*: physiological map and its associated cell bodies and terminals from *control case 1934* were warped to a rectangular shape. Warping of the physiological maps and associated lesions were done similarly for each experimental case in this report. *C*: to obtain the hypothetical proportion of cell bodies and terminals in the lesion, the warped map and lesion from each experimental case were superposed on the warped distribution of the control case.

were ~50% of the M1 DFL. Multiple linear regressions found that the degree of disruption of M1-PMv connectivity is a nonsignificant ($P = 0.1763$) predictor of physiological changes in PMv, whereas the proportion of the M1 DFL destroyed by the lesion is a statistically significant predictor ($P = 0.0008$). Thus standard model building paradigms (forward selection, backward elimination, and stepwise selection) (Draper and Smith 1998) all converge to a single explanatory variable describing postinfarct alterations in the PMv DFL. This variable is the proportion of M1 DFL destroyed by the lesion.

DISCUSSION

This study's aim was to evaluate the effects of small lesions in the M1 DFL on neurophysiological maps in the PMv DFL. In sharp contrast to previous studies targeting 57–97% of the M1 DFL that resulted in proportional increases in the PMv DFL, the present results demonstrated consistent *decreases* in the PMv DFL after small lesions comprising <50% of the M1 DFL. Changes in PMv were independent of lesion location in M1 with respect to patterns of connectivity between M1 and PMv. Using standard model-building techniques, we found that the proportion of the M1 DFL destroyed was a better predictor of PMv plasticity than the location of the lesion with respect to PMv-M1 connectivity.

It is possible that the results were partially dependent on the time of reevaluation of PMv DFL after the lesion (12 wk). This time point was chosen mainly based on human data clearly showing that the bulk of the fast spontaneous recovery occurs within the first 12 wk (Duncan and Lai 1997). Spontaneous recovery then appears to slow down and even plateau in cases with milder initial deficits. However, recent studies have suggested that the cortical reorganization associated with behavioral recovery is very dynamic and that the topographic organization can be dramatically different at different time points (Schmidlin et al. 2004). It is yet a possibility that smaller lesions result in a different temporal profile for cortical reorganization. In that regard, it should be noted that the behavioral recovery after smaller lesions is faster than what is observed after larger lesions (Friel et al. 2005; Heddings et al. 2000).

Relationship between M1 lesion size and PMv reorganization

The relationship we found between lesion size in M1 and PMv reorganization is reminiscent of Lashley's classic description of the relationship between cerebral mass and behavioral change (Lashley 1929, 1930). According to this hypothesis, lesion size is generally assumed to be associated with the severity of deficits, whereas lesion location is related to the specificity of deficits. Lashley also proposed the concept of equipotentiality, suggesting that each portion of a given cortical area is able to encode or produce behavior normally controlled by the entire area. In that vein, after smaller lesions, such as in $M1_{rl}$ or $M1_{cm}$, the surviving M1 tissue could potentially subserve the recovery of function. In that case, reorganization in distant, interconnected cortical areas would be a more "*passive*" process resulting

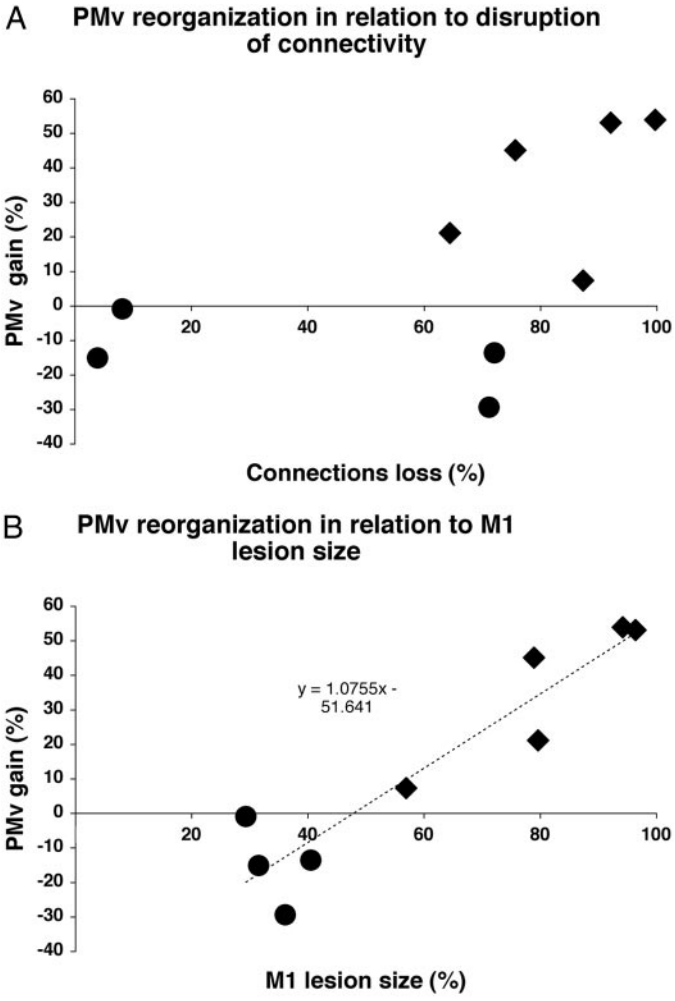

FIG. 4. Factors initiating PMv reorganization after M1 lesion. *A*: relationship between the predicted disruption of connectivity of PMv with M1 and physiological reorganization in PMv. Based on cortical connections between PMv and M1 in naïve squirrel monkeys, the potential impact of the lesions in M1 were estimated in relation to the physiological reorganization found in PMv. In general, this relationship was not strong. PMv connections were derived as the average of the proportion of cell bodies and terminals. Circles are used for the cases described in the current experiment (4A1C; 103E; 4B; 1940); diamonds are used for cases with larger lesions (Frost et al. 2003). *B*: relationship between PMv reorganization and lesion size in M1. Percent change in PMv DFL 12 wk postinfarct as a function of the percent anatomical loss of M1 DFL. Animals with partial lesions (present study; circles) are combined with animals that sustained larger lesions (from Frost et al. 2003); diamonds). Whereas these latter animals showed an increase in PMv DFL, animals with smaller lesions showed a decrease. A diagonal dotted line shows the linear regression associated with the corresponding equation.

from the loss of intercortical connections. This reorganization could be compared with a "sustained diaschisis" of PMv. After larger lesions, reorganization of the adjacent tissue may not suffice for normal motor execution. Thus learning-associated reorganization would need to take place elsewhere, resulting in greater PMv DFL expansion. Accordingly, in rats, the contralesional cortex is thought to be involved in behavioral recovery only after large lesions (Biernaskie et al. 2005). Our current set of data similarly suggests that lesion size is a major factor involved in the initiation of some of the vicarious processes that purportedly play a role in recovery from CNS lesions.

Along these lines, the expansion of the PMv DFL might be triggered by compensatory behavioral demands generated by the lesion. Motor learning has been found to be essential for the expansion of cortical motor representations (Plautz et al. 2000). In addition, human neuroimaging studies have shown that an increase in task difficulty results in an increased cortical activation, including the ipsilateral cortex (Winstein et al. 1997) and that attention to a task results in greater cortical activation in relation to that task (Johansen-Berg and Matthews 2002). After stroke, behavioral recovery with increased performance on a task was associated with a decrease of cortical activation to patterns more closely resembling those of normal subjects (Wittenberg et al. 2003). Similarly, in our small lesions with mild and transient motor deficits, the increase of task difficulty resulting from these deficits might not be high enough to require the increased activation of premotor areas.

In comparing results from ICMS and neuroimaging studies, one should bear in mind that these are very different and perhaps complimentary techniques that reveal different aspects of cortical function. As used here, ICMS-derived motor representations are defined by movements evoked at threshold current levels. Movement-related activation patterns using functional magnetic resonance imaging (fMRI) or single-unit recordings in awake behaving animals may not necessarily follow the same trends observed with ICMS in anesthetized animals.

Small lesions, such as the ones used in the present experiment, result in relatively mild and transient deficits (Friel et al. 2005). Such mild deficits might only require minor postlesion learning (or compensatory motor strategies) for which the intact, adjacent neuronal network would be sufficient. It was suggested that the smaller lesion would not result in sufficient behavioral deficits to initiate the elaboration of novel, perhaps more effective, compensatory behavior (Friel and Nudo 1998). In regard to this, the animals in the present experiment did not undergo any specific rehabilitative training after the lesion.

Whereas our data do not specifically address these behavioral issues, they do underline the complex interactions between various components of the cortical motor system. Compensatory changes that occur in regions distant from the site of an injury are not exclusively based on rules of cortical connectivity. Our data specifically show that initiation of the expansion of the DFL in PMv is not triggered simply by a disruption of the majority of PMv's connections with the M1 DFL. Rather, lesion size, independent of connectivity, seems to linearly predict PMv reorganization. However, due to the relatively small sample sizes, this linear fit is merely suggestive rather than conclusive. Multiple processes driving remote changes may yield more complex relationships as more data become available. These results extend our understanding of the fundamental rules of cortical reorganization taking place in the CNS after ischemic lesions as might occur in stroke. The unraveling of these principles is essential to our understanding of postinjury recovery and might provide rationale for clinical interventions.

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