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Dynamic organization of primary motor cortex output to target muscles in adult rats
II. Rapid reorganization following motor nerve lesions

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Summary. In the accompanying paper (Sanes et al. 1989), we demonstrated that the map of motor cortex (MI) output was reorganized when examined 1 week to 4 months after a motor nerve lesion in adult rats. The present experiments measured the extent of functional reorganization that occurs within the first hours after this lesion. Shifts in MI output were examined by testing the effect of stimulation at a site in MI vibrissa area before and up to 10 h after nerve section of the branches of the facial nerve that innervate the vibrissa. Immediately following nerve transection, no movement or forelimb EMG activity was evoked by intracortical electrical stimulation within the vibrissa area. Within hours of the nerve transection, however, stimulation elicited forelimb EMG responses that were comparable to those obtained by stimulating within the pre-transection forelimb area. Remapping of MI after nerve transection indicated that the forelimb boundary had shifted about 1 mm medially from its original location into the former vibrissa territory. Forelimb EMG could be evoked for up to 10 h within this reorganized cortex. These results indicated that the output circuits of MI can be quickly reorganized by nerve lesions in adult mammals.

Key words: Motor cortex – Somatotopic representations – Peripheral nerve injury – Neural plasticity – Motor control – Rat

Introduction

The relationship of the cerebral motor cortex (MI) with its target muscle groups is modified by mixed or motor peripheral nerve lesions in developing or adult animals (Donoghue and Sanes 1987, 1988; Sanes et al. 1988; Sanes et al. 1989). The amount and form of the cortical reorganization are roughly comparable in animals that received nerve lesions either in the neonatal period or when mature. With intracortical electrical stimulation techniques, areas of MI that were disconnected from the periphery formed output relationships with different muscle groups. There appears to be an orderly reorganization, insofar as only the muscle groups that are normally represented in adjacent areas of MI become represented within disconnected regions. Reorganization of MI has been shown to occur as early as 1 week following a motor nerve transection and is maintained for at least 4 months (Sanes et al. 1989). In addition, there does not appear to be any substantial difference in the quality and quantity of reorganization within these time periods.

The mechanism by which MI assumes relationships with a new group of muscles, and the location of these changes, is uncertain. The maintenance of the reorganized representation pattern in MI for up to 4 months might suggest that morphological synaptic rearrangement or axonal growth coupled with new synapse formation, phenomena that appear to occur within the adult CNS (Raisman and Field 1973; Tsukahara and Fujito 1976), are substrates for MI reorganization. Alternatively, the establishment of novel relationships between MI and muscles within 1 week of a motor nerve injury (Sanes et al. 1989) might suggest that a different substrate supporting ongoing changes in the relationship between MI and its target muscles normally exists. This mechanism could involve unmasking or activation of existing synapses in pathways that ultimately project to various target motor neuron pools. Activation of normally silent synapses is also known to occur within the CNS (Dostrovsky et al. 1976; Metzler and Marks 1979; Nelson et al. 1979).

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The existence of long horizontal axons within MI (DeFelipe et al. 1986; Ghosh and Porter 1988) and the collateralization of pyramidal tract axons throughout their course to and through the spinal cord (Endo et al. 1973; Shinoda et al. 1976, 1979, 1986) could provide the morphological substrate for synaptic unmasking as the mechanism for reorganization of MI output networks.

The occurrence of very rapid shifts in MI output relationships would support the hypothesis that a substrate mediating dynamic changes in the relationship between MI and muscles normally exists. In the present experiment, we examined, in individual animals, the time of onset and the extent of reorganization of MI muscle and movement representations that occur within a few hours following a motor nerve lesion. Preliminary portions of these data have been previously reported (Donoghue et al. 1987; Sanes et al. 1988).

Material and methods

Surgical preparation

Movement and muscle representations of the frontal cerebral cortex were examined in 12 adult female albino rats (Sprague Dawley) weighing 150 to 250 g. The general surgical and post-experiment histological procedures were the same as those described in the preceding paper (Sanes et al. 1989).

In order to record the forelimb electromyogram (EMG) in relation to MI stimulation, the biceps brachii and wrist extensor muscles were implanted with two sets of stranded, Teflon-coated stainless steel wires (25 μm, 1–2 mm exposed tips). These were inserted into the muscle either percutaneously or under direct observation following surgical exposure of the muscle. Appropriate placement of the electrodes was verified by observing the movement elicited with electrical stimulation of the muscle through the implanted electrode. The buccal and mandibular branches of the facial nerve were transected while the rat was in a stereotaxic frame and after the intracranial stimulating electrode was implanted at an MI site.

Time course of changes in muscle activity

MI was mapped using intracortical electrical stimulation techniques similar to those described in the preceding paper (Sanes et al. 1989) to determine the areas from which vibrissa and forelimb movements were evoked. Sites were stimulated with 45–60 μA of current to find the distinctive areas from which forelimb movement and EMG and vibrissa movements were evoked. Typically, fewer than 20 electrode penetrations (11 to 19 sites) were used to identify the border between the MI forelimb and vibrissa regions. Following the initial mapping, the stimulating electrode was implanted 1.7 to 1.9 mm below the surface of the cerebral cortex at a site within the low threshold vibrissa area from which brisk vibrissa movements were evoked. Electrical stimulation with single stimulus trains at this site did not evoke forelimb movements or observable forelimb EMG at a fixed current intensity of either 45 or 60 μA. This site was termed the test site. The test site was located no more than 500 μm medial to the border of the forelimb and vibrissa output region. The site was judged not to be connected functionally to the forelimb muscles since neither forelimb movement nor wrist extensor or biceps muscle activity could be evoked at the currents employed. In six animals, the forelimb movements and EMG evoked by stimulating at the test site were monitored for up to 1 h before and for 4 to 10 h after acute transection of the facial nerve branches innervating the vibrissa. During this period, the EMG was sampled at 15 or 30 min intervals. Three other animals were observed for a shorter period after the nerve transection and then were remapped (see below) to examine the extent of rapid MI reorganization.

In two of the rats studied, a linear array of three electrodes was implanted in MI after determining the border between the vibrissa and forelimb areas. The electrode array was placed such that one of the electrodes (the *test site* electrode) was located medial to the vibrissa-forelimb border. The other two electrodes were located within either the vibrissa or the forelimb low threshold zone. The EMG elicited by electrical stimulation through these electrodes was recorded for 4 to 10 h as described above.

Extent of short-term MI representation shifts

In three rats, a more detailed MI map (57, 55 or 51 points, spatial resolution of $\sim$250 μm) was obtained prior to the facial nerve transection. Then the electrode was placed medial to the vibrissa-forelimb border at a site from which only vibrissa movements were evoked, and the facial nerve was transected. When forelimb muscle activity was evoked reliably from the biceps and wrist extensor muscles at the test site (in these animals, 1 to 2 h following the nerve transection), MI was remapped (42, 44, or 48 points). One half of the penetration sites for the remapping were identical to sites that had been previously mapped. The other half of the remapping sites were no more than 100 μm away from previously mapped points. These procedures were used to sample identical sites and also to sample sites that were not damaged previously by electrode penetrations. These rats were among those mentioned above in which stimulation at single MI sites in the vibrissa region was evaluated for forelimb movements after facial nerve section.

Data acquisition and analysis

Muscle activity was amplified (Neurodata, Grass Instrument Co.) at a gain of 10 k, filtered (100 Hz to 4 kHz bandpass) and 150 ms epoches were digitized (4 kHz, each channel) and rectified using a Metrobyte analog to digital board and an IBM AT computer. Ten trial averages of this record were stored and the integrated activity of the average between 0 and 100 ms after onset of the intracortical stimulus was used as the quantitative measure of muscle activity. Background noise on the EMG, considered for 50 ms before the stimulation, was subtracted from the averaged response. The amplitude of the EMG signal was computed in off line analysis in arbitrary units that were the same for all measurements. This number was used to determine the *amount* of muscle activity which was calculated as integrated activity units over the 100 ms sample period. This activity is expressed throughout as a percentage of the maximal amount recorded for that muscle during the entire course of the experiment. In two cases (MRM3,4) the EMG was collected using a Modular Instruments interface and software. Arbitrary EMG units were multiplied 10 times to give scalar values similar to those collected by the other system.

Results

Properties of the normal forelimb area

Prior to the facial nerve transection, forelimb muscle activity was evoked from 108 of the 275 (39.3%)

sites examined with the fixed current of 45 or 60 μA. Either biceps and/or wrist extensor muscle activity were evoked at all sites from which forelimb movements were evoked. Typically, the forelimb EMG at threshold currents consisted of two components. The latency of the evoked biceps or the wrist extensor muscle responses following stimulation ranged from 10 to 15 ms.

Temporal course of reorganization at single MI sites

This section describes data from animals in which (1) an electrode was placed medial to the vibrissa-forelimb border at a vibrissa movement site from which no forelimb muscle activity could be evoked, (2) the facial nerve was transected, and then (3) the evoked forelimb EMG from stimulation at the vibrissa area test site was observed for up to 10 h. In eight of the nine animals tested, there was no evoked forelimb EMG when the test site was stimulated during a 0–100 min period prior to the facial nerve transection. In the ninth animal, there was a very small evoked response that was only detected during the post-experimental analysis of the averaged EMG. This animal was included because the nerve transection eventually resulted in a persistent and large increase in the elicited forelimb EMG from the test site.

Within 4 h following the facial nerve transection, a substantial EMG was evoked from the biceps and wrist extensor muscles from stimulation at the test site of all animals (time to onset, 106.88 ± 24.46 min [mean ± SEM] for wrist extensors; 90.0 ± 16.58 min for biceps, Figs. 1 and 2). The onset of an evoked EMG from the two forelimb muscles was usually, but not necessarily, concurrent (Fig. 2). In eight of the nine animals, when an increase in the forelimb EMG was first observed from stimulation at the test site, the magnitude of the evoked forelimb EMG was comparable to that previously observed within the low threshold forelimb area. In the remaining animal, the magnitude of the muscle activity elicited from stimulation at the test site resembled responses evoked from the forelimb-vibrissa border area in nontransected animals; the size of the evoked responses was about 20% of the maximum magnitude evoked from the low threshold forelimb area prior to transection of the facial nerve. However, in this animal too, the elicited forelimb EMG increased to sizes comparable to those observed within the low threshold forelimb zone 120 min after the nerve lesion.

The amount of muscle activity evoked from the test site fluctuated over time (Figs. 3 and 4A). The fluctuations in the biceps and wrist extensor muscles

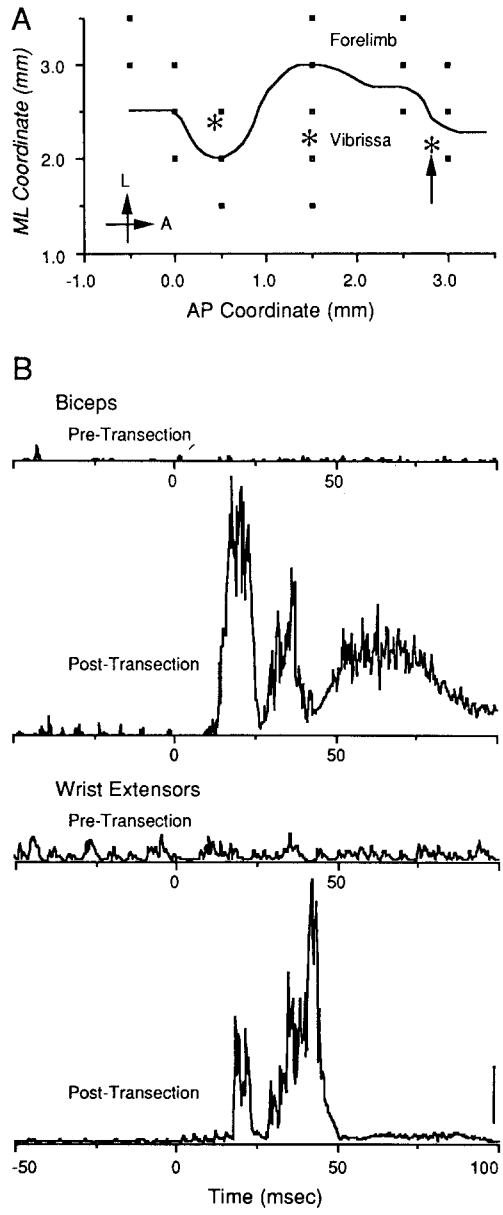

Fig. 1A,B. Evoked forelimb EMG from the MI vibrissa area following the facial nerve lesion. **A** Cortical surface map of animal AVS14 illustrating the location of the electrode penetrations (dots) made prior to the nerve transection. Coordinate (0,0) corresponds to bregma. The solid line represents the border between the low threshold forelimb and vibrissa movement zones. The forelimb zone is located lateral (up on graph) to the vibrissa zone. The location of three electrodes implanted after the initial mapping, and left in place for the remainder of the experiment, are marked by asterisks. **B** Muscle activity recorded from biceps (upper two traces) and wrist extensors (lower two traces) by stimulating at the site marked by the arrow in **A**. The records were taken prior to (upper trace of each set) and 1 h after (lower trace of each set) the facial nerve transection. Each trace is the rectified EMG average of 10 stimulus trains. Calibration bar is 200 units for all traces

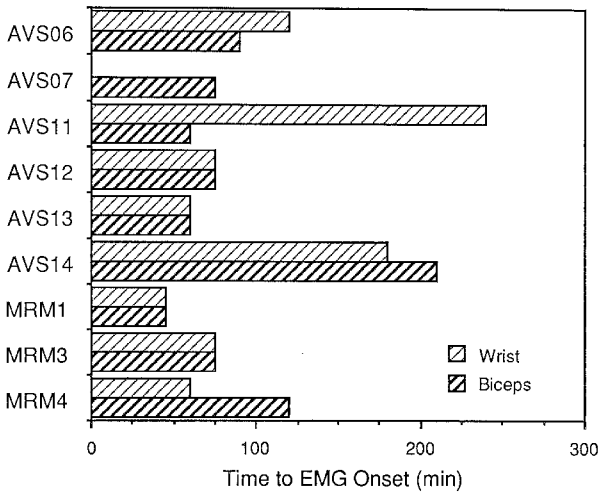

Fig. 2. Time-to-onset of forelimb muscle activity in the normal vibrissa region after facial nerve lesion. Time of evoked muscle responses to stimulation from the test site in the former low threshold MI vibrissa region of each animal ranged from 60 to 240 min. The onset of biceps and wrist extensor activation was not necessarily coincident. The wrist extensor electrode of animal AVS07 malfunctioned

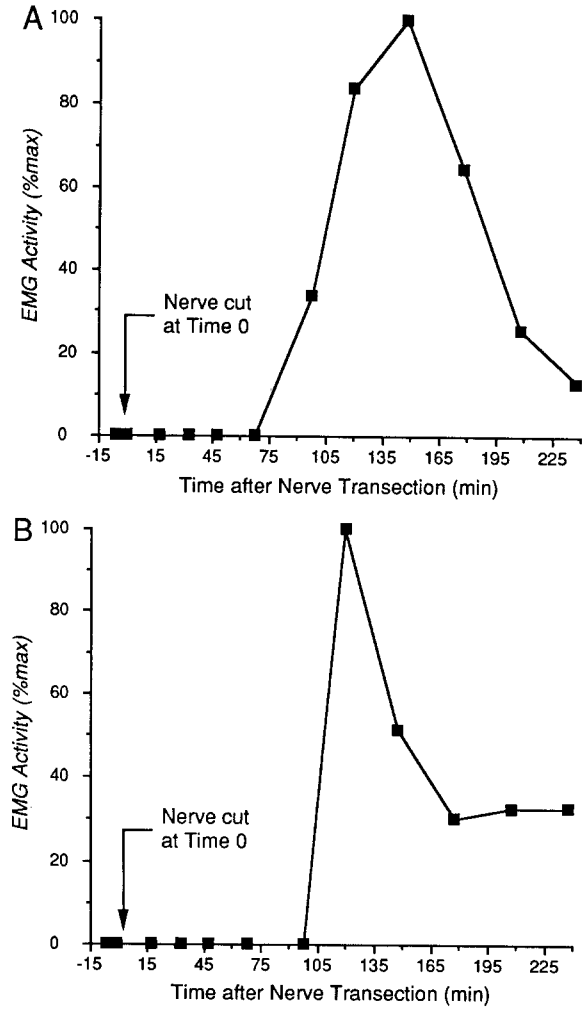

Fig. 3A,B. Time course of forelimb muscle responses from vibrissa site in MI. The onset and fluctuation of the biceps (**A**) and wrist extensor (**B**) EMG evoked from stimulation at a single site in MI in animal AVS06; the site was identified as originally being within the low threshold vibrissa zone and did not ostensibly represent the forelimb musculature before the facial nerve transection (time 0). A response was evoked in the biceps muscle (**A**) 100 min after the nerve transection. Elicited muscle responses persisted for 240 min after the nerve transection (the experiment was terminated after the last measurement). Each value represents the integrated and averaged muscle activity from 10 stimulation trains. The values are normalized to the highest response obtained from stimulation at that site

were weakly correlated in three animals ($r \geq 0.52-0.63$, $p \leq 0.05$) and uncorrelated in two animals. (Only five animals were observed for a sufficient time to allow for these correlations.) At the conclusion of the experiment, the magnitude of the EMG was typically lower than the maximum response evoked from that site (biceps and wrist muscles combined, $34.76 \pm 11.17\%$ of the maximum response recorded from the test site). In the animal in which some forelimb muscle activity was evoked from the test site prior to the transection, the EMG evoked 5 h after the nerve transection was still twice the amount observed prior to transection. We found no relation between fluctuations in the evoked EMG and either body temperature or the periodic supplemental injections of ketamine.

Fluctuations in the evoked forelimb activity over time also occurred in the low threshold forelimb zone. In two of the nine animals with the facial nerve transection (see Methods), an additional electrode had been chronically placed in the forelimb movement representation, and forelimb muscle activity elicited from this site was also evaluated for the duration of the experiment. Within the low threshold forelimb zone, evoked responses from biceps and wrist extensor muscles exhibited a wide range of response magnitudes, and these fluctuations were not correlated with each other (Fig. 4B). It appeared that the forelimb muscle activity evoked from the low threshold forelimb area in the animal illustrated in Fig. 4B reached minima 45 to 90 min after the transection. This was not concurrent with the onset time of evoked forelimb muscle activity from the test site, but preceded it by about 100 min.

In order to rule out the possibility that the borders of MI output zones shift spontaneously and therefore are unrelated to nerve transection, we monitored, in three animals, the forelimb EMG evoked from a single site in the low threshold vibrissa area for 10 h. In these animals, every experimental parameter was identical to those used for the

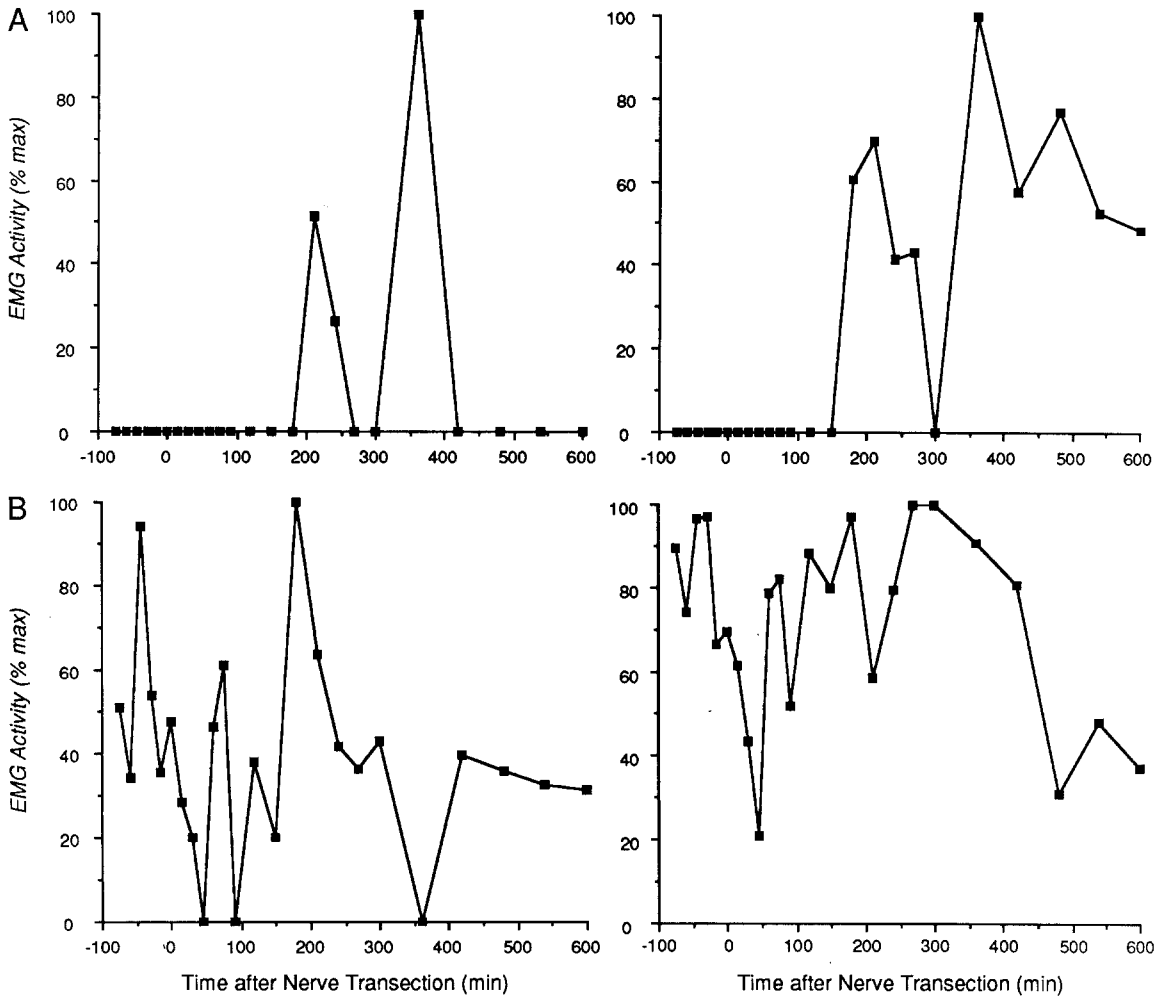

Fig. 4A,B. Time course of evoked muscle responses from MI before and after a facial nerve transection. Records from animal AVS14. **A** The evoked EMG is shown from biceps (left) and wrist extensor (right) muscles from a test site in the former vibrissa zone (marked by arrow in Fig. 1) from which stimulation evoked vibrissa but no forelimb movements over a 90 minute period prior to the facial nerve lesion. Note the fluctuations, some with opposite trends in the evoked EMG of the two muscles. **B** Biceps (left) and wrist extensor (right) muscle activity evoked from the normal forelimb zone (the site indicated by the left-most asterisk in Fig. 1) recorded immediately after samples in the vibrissa area. These EMGs also fluctuated during repeated testing

nerve transected animals, except for the actual transection of the facial nerve. In no instance was forelimb muscle activity evoked during the 10 h period in which the test site within the low threshold vibrissa zone was stimulated after sham facial nerve lesion.

Extent of short-term MI reorganization

The extent of MI output reorganization following a facial nerve transection was assayed by mapping the same or nearby MI sites in three rats before and after the facial nerve transection. In all of these animals, forelimb muscle activity was elicited from the test site 75 to 120 min following the nerve transection. Figure 5 illustrates the onset of the evoked forelimb EMG from one of these animals. The forelimb-vibrissa border determined before and after the nerve transection is shown in Fig. 6 for all three animals. The set of electrode penetrations, completed 4 to 5 h after the facial nerve lesion, indicated that the border of the area from which forelimb movements could be elicited shifted medially with respect to the original low threshold forelimb border. The combined data from the three animals showed that the forelimb movement border shifted medially a maximum of about 1 mm after the nerve transection. The size of the newly formed part of the forelimb MI representation was 0.90 mm^2, 2.01 mm^2 and 2.4 mm^2 in each of the three animals.

The magnitude of the EMG evoked from both forelimb muscles in the normal low threshold and expanded forelimb area was compared in these three

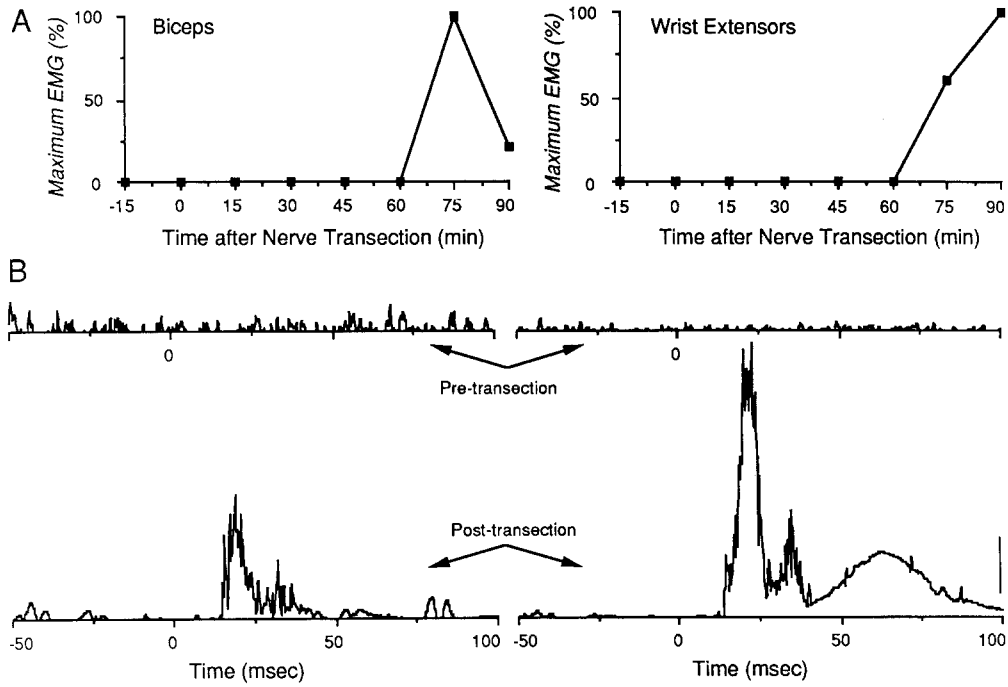

Fig. 5A,B. Time course of EMG onset after facial nerve transection from animal MRM1. EMG responses were evoked by stimulation at the vibrissa region test site from the biceps and wrist extensor muscles within 75 min after the facial nerve transection. **A** The time course of the EMG responses for 90 min after the transection. **B** Average muscle responses from the test site just before (time 0 in A, upper records) and 75 min after (lower records) from the biceps (left) and wrist extensor (right) muscles. The EMG scale is 300 units

animals for both of the recorded muscles, yielding a total of six comparisons (Fig. 7). The amount of muscle activity evoked from the expanded zone was similar to the EMG elicited from the normal forelimb zone before the nerve transection in four instances. In the two other comparisons, the EMG from the expanded area was less than that elicited from the normal area before the transection ($p \leqslant 0.05$). The total amount of forelimb EMG elicited after the nerve transection was the same in three, less in one, and more in two comparisons of muscle activity elicited before the transection.

The enlargement of the forelimb area after facial nerve transection and the concomitant changes in the magnitude of the evoked EMG can be seen in a three-dimensional representation of muscle activity elicited from stimulation at MI sites in one animal before and after the nerve transection (Fig. 8). In this animal, the overall forelimb EMG increased after the facial nerve transection, and the extent of MI from which forelimb muscle activity could be elicited enlarged medially and posteriorly.

Discussion

This study indicates that MI output (i.e., the motor map) reorganizes in adult rats within hours after one part of MI is disconnected from its target muscles. In this case the area of MI that participated in controlling one general set of muscles rapidly assumed control over a very different set of muscles. Continuous monitoring of the effect of electrically stimulating MI output neurons revealed that the shift in organization was abrupt and maintained for several hours. The present data coupled with the results of the preceding report on long-term changes of MI output organization (Sanes et al. 1989) could indicate that shifts in MI output control are established soon after nerve injury and maintained relatively intact until new reorganizational stimuli impinge upon MI.

Are MI representation shifts related to the occurrence of the nerve transection?

Our previous work concerned with MI reorganization (Donoghue and Sanes 1987, 1988; Sanes et al. 1988; Sanes et al. 1989) has not addressed the issue of whether the alterations in MI output organization were spontaneous shifts in output control or were causally related either to withdrawal of somesthetic inputs to MI or to an uncoupling of MI from its target muscles. In those experiments, individual animals were mapped once, and comparisons of MI

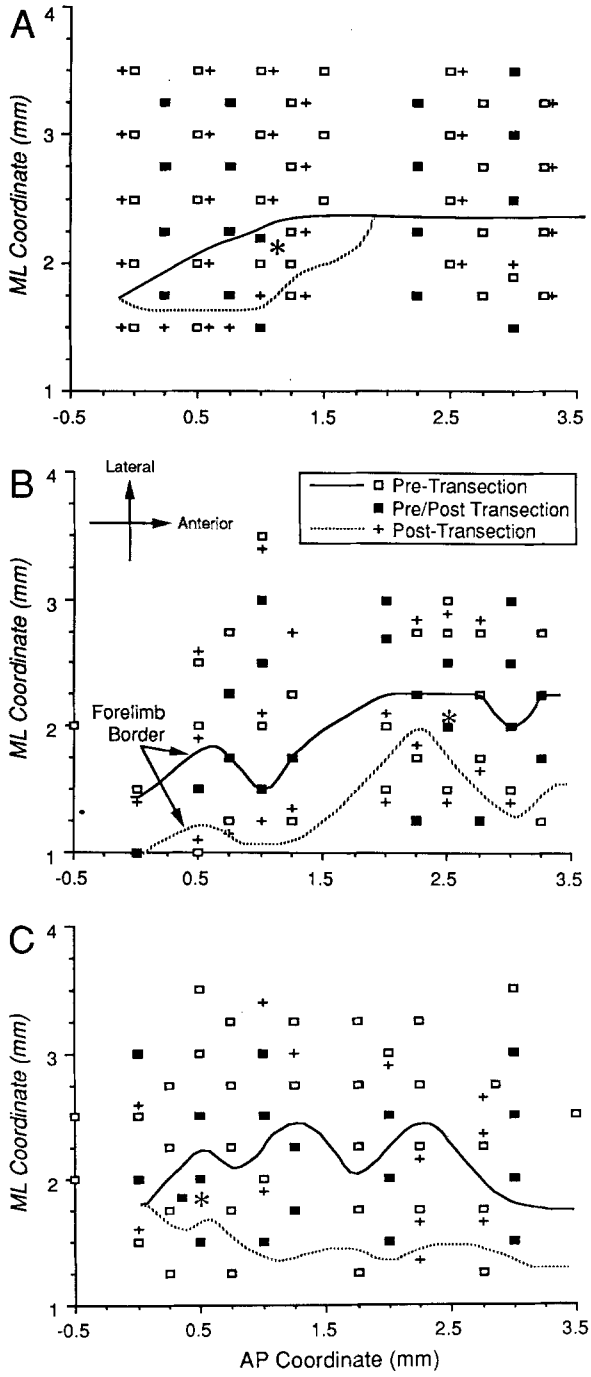

Fig. 6A–C. Expansion of the MI forelimb region after facial nerve transection. Cortical surface maps of MI from three rats (**A** MRM1, **B** MRM3, and **C** MRM4) illustrating the mapped border of the forelimb movement zone before and after the facial nerve transection. The pretransection medial border of the forelimb area (solid line) is more lateral than the posttransection medial border of the forelimb zone (dashed line). Each square (open or closed) and cross represents an electrode penetration before and/or after the nerve transection. In each graph, the site marked by an asterisk indicates the location of an implanted electrode used to monitor when, after the facial nerve transection, forelimb muscle activity was evoked from the former vibrissa region

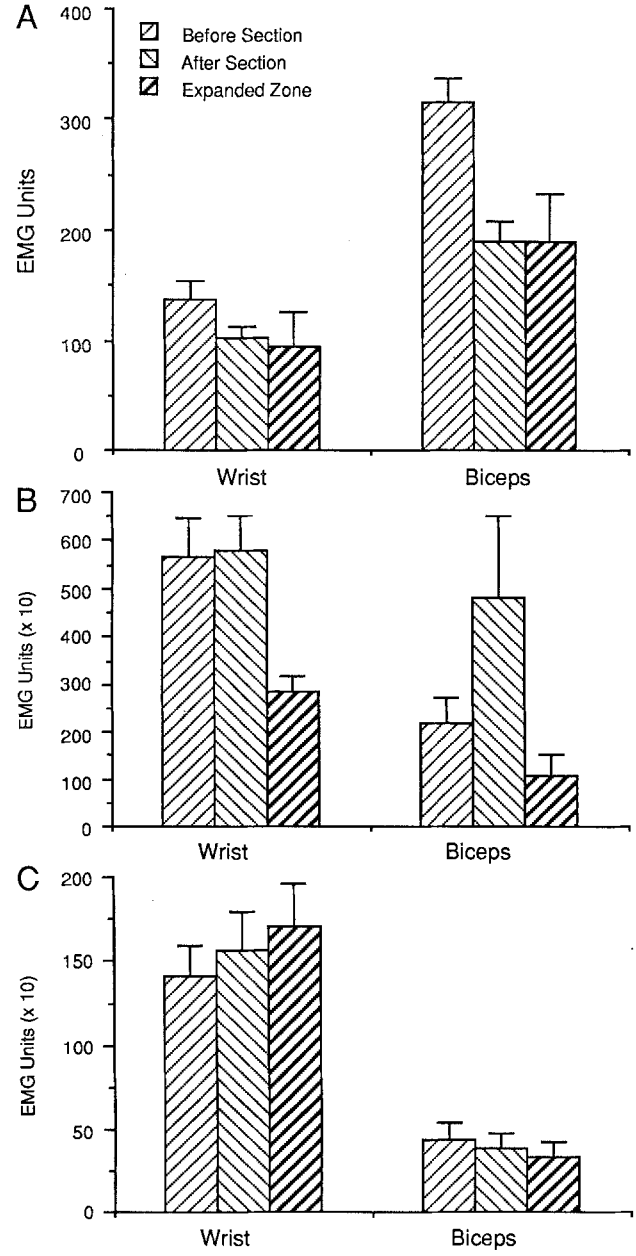

Fig. 7A–C. Comparison of evoked muscle responses before and after the facial nerve transection. The mean (±SEM) EMG from all sites in either the normal forelimb zone, before and after the transection, or the expanded region of forelimb zone was calculated from animals MRM1 (**A**), MRM3 (**B**), and MRM4 (**C**). Integrated EMG is expressed in arbitrary units

output relationships were made between normal animals and those with nerve lesions. In contrast, in the current experiments, single sites, or large portions of MI, were examined immediately before and for several hours after a motor nerve lesion. The results indicated a close temporal correspondence between shifts in MI output organization and facial nerve transection. Furthermore, in animals in which

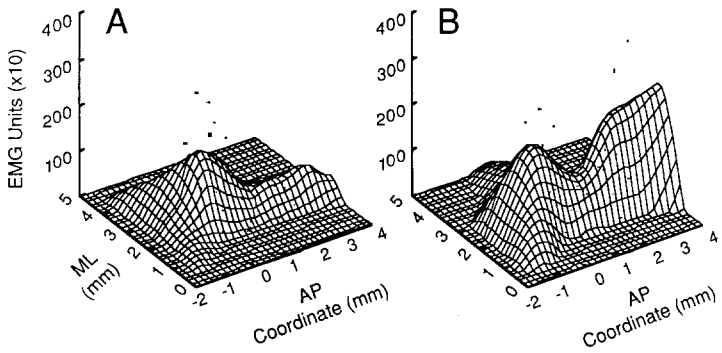

Fig. 8A,B. Magnitude of the evoked EMG from MI. A three-dimensional representation of the muscle responses elicited from stimulation at all points within MI before (**A**) and after (**B**) the facial nerve transection in animal MRM4. The plane of the graph represents the cortical surface, the z-axis represents the magnitude of the evoked EMG from the wrist extensor muscles. The border of the MI zone from which the wrist extensor EMG could be evoked was located medial and posterior to the original border after the facial nerve transection. This graph was constructed with a locally weighted smoothing algorithm using multiple regression on the available points. Data points appear as dots above and within the EMG contour. The EMG activity was not normalized and is expressed in equivalent arbitrary EMG units for both contours

MI was assayed for prolonged periods without the nerve transection, there was no evidence of major spontaneous shifts in MI output patterns. This latter result is in accord with previous results that have concluded that MI movement representations of individual limbs of normal baboons are generally stable over months (Craggs and Rushton 1976).

Fluctuations in the amount of muscle activity evoked from single MI sites did occur in the forelimb area, outside of the region where one would expect there to be a direct effect of the lesion. A simple explanation for the fluctuations could be that they were related to general and uncontrolled modulations in the metabolic condition of the rat. Many of these variables cannot be measured or controlled. However, it did not appear that the EMG fluctuations were related to changes in body temperature or injection of anesthetic. Furthermore, the fluctuations in one muscle were not necessarily correlated with those of the other forelimb muscle, thereby suggesting that local neural and not general metabolic conditions are the important mediators of the level of muscle response to MI stimulation. Another contribution to response fluctuation may be derived from stimulation of the cortex itself. Early work indicated that repeated stimulation of MI could modify movements evoked by cortical surface stimulation (Brown and Sherrington 1912; Leyton and Sherrington 1917). However, using intracortical stimulation we routinely obtain in normal rats the same movements at sites that are mapped at different times during an experiment (Donoghue and Sanes 1988).

Cues for MI reorganization

The nature of the events following the facial nerve transection that signal MI reorganization are uncertain. Candidate mechanisms that could trigger cortical output reorganization might include trophic factors and modification of sensory inputs to MI. At the spinal level, trophic factors have been suggested to play a role in synaptic reorganization (Cope et al. 1980). Additionally, peripheral motor nerve transections result in numerous changes at the level of motor neuron and the transected axon (Raivich and Kreutzberg 1987; Tetzlaff et al. 1988). Some of these changes occur within the time frame necessary to trigger rapid MI reorganization. However, the specificity of such trophic changes is questionable. Although the release of a humoral factor subsequent to nerve injury could conceivably reach MI in a short period of time, the substance would likely be perfused in a nonspecific fashion. Thus, it would be difficult to conceive of a trophic substance acting as a specific cue for MI reorganization.

Another mechanism to trigger MI output reorganization could be alterations in sensory inputs to MI. After facial nerve transection, the "tone" of the vibrissa is abnormal, probably leading to reduced, but certainly different, sensory inputs. If these inputs have an influence on MI neurons in the rat, as recently described (Hummelsheim and Wiesendanger 1986; Sievert and Neafsey 1986), then it is possible that withdrawal of a tonic or periodic input to MI output cells could trigger MI reorganization.

Possible mechanisms for MI reorganization

These studies were initiated to provide evidence for mechanisms related to the control of synaptic efficacy that could serve as a potential means to adjust the relationship between MI and its target muscles. Since changes in MI output characteristics were observed soon after the facial nerve transection, new axonal growth, and then formation of new synaptic connections, probably does not account for immediate changes in MI organization. Morphological alterations within the brain have been measured in terms of days rather than hours (Raisman and Field 1973). It is also unlikely that the newly expanded representations were produced by revealing extant high threshold output representations by nerve section. The same current intensities were employed over the course of an experiment and forelimb movements and, more importantly, muscle activity was not evoked by stimulation of the vibrissa test sites until the motor nerve was transected. At least when measured several days after nerve transections, it appears that the currents required to evoke forelimb movements in the expanded regions are not different from those required in the normal forelimb area (Sanes et al. 1989). A more parsimonious explanation for MI reorganization could be that there was a change in the efficacy of already existing pathways and synapses. Since stimulation within this region normally fails to elicit any forelimb muscle activity, these putative synapses cannot be, or are only weakly, activated by stimulation within the MI vibrissa area. However, within a few hours, similar stimulation does evoke responses from forelimb muscles. Unmasking of preexisting, but functionally ineffective, synapses seems to occur within the CNS (Dostrovsky et al. 1976; Nelson et al. 1979; Devor and Wall 1981).

Instead of unmasking-like phenomena mediating MI representation plasticity, it is also possible that the nerve lesion altered membrane excitability. Thus, a larger electrical stimulation map of remaining areas could be obtained because the nerve transection lowered the thresholds to elicit movements in now more easily excitable output neurons located at a relatively greater distance from the stimulating electrode. The features of the maps generated before and after the facial nerve injury do not support this supposition. Before transection there was little evidence of a nearby forelimb site that could be activated by higher levels of stimulation. In a few cases tested forelimb movement could not be evoked (at $\leq 60\ \mu A$) from the vibrissa test sites. If generalized excitability changes occurred, the forelimb EMG would be expected to fall off with distance and the spread of effect would be expected to extend in all directions if cells were simply more excitable. However, movements of the stimulating electrode of about 250 μm could result in abrupt shifts in the type of movements that were evoked either in normal MI or in MI after the nerve transection. Note, for example, in Fig. 6A that parts of the forelimb area border remained unchanged after nerve transection. A generalized cell excitability change would also be expected to increase the amount of activity obtained from the normal forelimb representations. As shown in Fig. 4, this did not occur. For these reasons, we favor the explanation that the alteration in MI organization that occurs after nerve injury is the result of a change in the synaptic strength of connections somewhere in the links formed within the cortex or along the path to the target muscles.

Nerve injury may not be the only stimulus that reorganizes cerebral cortical representation patterns. It appears that for sensory cortices, alterations in afferent input are sufficient to induce rearrangements of sensory representations (Hubel and Wiesel 1965; Sherman and Spear 1982). Alterations in sensory inputs to MI could also contribute to the guidance and maintenance, in addition to the cueing, of MI output reorganization. In the monkey, there is a close correspondence between the afferent and efferent organization of MI (Rosén and Asanuma 1972; Strick and Preston 1982). Any alteration in this relationship could trigger mechanisms designed to re-register input-output linkages of MI. Nerve injury results in reorganization of somatic sensory cortical representation patterns (Merzenich et al. 1983), and some changes appear to occur quickly enough to affect MI (Calford and Tweedale 1988). In addition, postinjury experience, from both afferent and efferent sources, may shape new sensory to motor links. However, Yumiya et al. (1979) found that switching of wrist flexor and extensor tendons did not alter MI input-output relationships. Nevertheless, it has been reported that afferent information is capable of reshaping the output relationships of MI. The role of afferent feedback in relation to MI maps was directly addressed by Gellhorn and Hyde (1953), who used surface mapping techniques to examine the MI representation in monkeys when the hindlimb was extended or flexed. A general conclusion of this work was that the extent of a muscle representation increased immediately when that muscle was stretched. Thus, the decrease in the size of the vibrissa representation could be due to decreased stretch of the vibrissa musculature when its motor innervation is removed. Increased sensory activity could have the obverse effect: repeated sensory stimulation of the glabella increases, for

prolonged periods, the excitability of MI neurons that were synaptically coupled to neurons in the facial nucleus (Brons and Woody 1980).

Site of reorganization

The current data do not directly address the location at which the relationship between MI output zones and their target muscles is altered. Reorganization may occur by changes in the connection strengths between parts of MI, or with other cortical areas, subcortically, at convergent sites of cortical outputs (Endo et al. 1973; Fetz et al. 1976; Shinoda et al. 1979, 1986), or within the subcortical structures themselves. Indeed, some subcortical structures have the capacity for changes in synaptic strength following nerve lesions (Wall and Egger 1971; Devor and Wall 1978, 1981; Nelson et al. 1979).

The form of the MI output reorganization might suggest that the motor reorganization is mediated by synaptic alterations occurring within MI. Output reorganization appeared to be restricted to cortically adjacent areas, as found in other studies (Donoghue and Sanes 1988; Sanes et al. 1989), even though areas such as the MI forelimb and vibrissa region have widely separated target motor neuron pools. Pyramidal tract neurons often project to multiple sites (Endo et al. 1973; Shinoda et al. 1979, 1986), but the extent of the projections is usually restricted to a few spinal segments (Shinoda et al. 1979, 1986). Pyramidal tract axons that have collaterals that spread to multiple motor neuron pools or premotor structures would not likely be a substrate for discrete motor control.

A more plausible explanation for the shifts in MI output control is that local MI circuits have existing, but normally weak or nonfunctional, synaptic relationships that are modified by nerve transection. This hypothesis would require the existence of horizontal connections between different MI areas and modification of these connections by nerve lesions or other reorganizational stimuli. Axons of MI pyramidal cells have horizontal collaterals of sufficient length to span more than one MI output zone (Donoghue and Kitai 1981; DeFelipe et al. 1986; Ghosh and Porter 1988). Thus, a modification in the synaptic strength of these intrinsic connections from the MI forelimb to vibrissa areas, for example, could alter the pattern of output organization from the deefferented cortex. One possible substrate for modulation of intracortical pyramidal tract axon collaterals would be local inhibitory GABAergic neurons. The existence and functional significance of such a circuit are supported by recent results suggesting that forelimb and vibrissa movements can be conjointly evoked from the low threshold vibrissa MI zone when the action of intrinsic GABAergic neurons is locally suppressed by iontophoretic application of bicuculline to the MI forelimb region (Jacobs and Donoghue 1988). Thus, strong excitatory connections intrinsic to MI may be masked by GABAergic inhibitory processes similar to those reported to shape the receptive field organization in visual and somatic sensory cortex (Sillito 1975; Dykes et al. 1984). The possibility that GABA effectiveness is normally modulated would be supported by recent reports that markers for GABA are reduced following decreases in afferent input to visual and somatic sensory cortex (Hendry and Jones 1986; Akhtar and Land 1987).

What is the role of a reorganized MI?

The functional implications of long-term (Sanes et al. 1989) and short-term reorganization of MI output in adult animals are not entirely clear. The alterations in MI output indicate that more cortical territory can be devoted to control of target muscles, and the strength of connection between MI and target muscles can be enhanced under appropriate circumstances. These findings would seem to indicate that more cortical neurons become associated with a particular set of muscles after one region of MI is disconnected from its target muscles. An implication of this supposition could be that the fineness of MI control of target muscles is adjustable. This notion assumes that an increase in the number of neurons associated with a behavioral function implies improvements in control of that function. Unfortunately, there is not any evidence to support this, and thus, it could be equally possible that an increased number of neurons controlling a behavior results in impaired performance.

Alterations in MI output patterns could mediate short- or long-term changes in motor function, especially regarding the acquisition of new motor skills. Accompanying improvements in motor skill are the obvious alterations in movement kinematics (Gershoni 1979; Schneider et al., in press), voluntary muscle activity patterns (Milner-Brown et al. 1975; Normand et al. 1982) and muscle reflex properties (Conrad, 1978; Neilson and Lance 1978). MI could be involved in all of these processes, especially since Sasaki and Gemba (1987) have described changes in the slow potentials recorded from MI when monkeys learn new movements. Moreover, Sakamoto et al. (1987) have demonstrated that long-term posttetanic potentiation, a process thought to be a model of learning in the nervous system, can be established in MI cells. However, definitive experiments describ-

ing the role of MI in motor learning have yet to be conducted.

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