

Use-Dependent Alterations of Movement Representations in Primary Motor Cortex of Adult Squirrel Monkeys

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This study was undertaken to document plastic changes in the functional topography of primary motor cortex (M1) that are generated in motor skill learning in the normal, intact primate. Intracortical microstimulation mapping techniques were used to derive detailed maps of the representation of movements in the distal forelimb zone of M1 of squirrel monkeys, before and after behavioral training on two different tasks that differentially encouraged specific sets of forelimb movements. After training on a small-object retrieval task, which required skilled use of the digits, their evoked-movement *digit* representations expanded, whereas their evoked-movement wrist/forearm representational zones contracted. These changes were progressive and reversible. In a second motor skill exercise, a monkey pronated and supinated the forearm in a key (eyebolt)-turning task. In this case, the representation of the *forearm* expanded, whereas the *digit* representational zones contracted. These results show that M1 is alterable by use throughout the life of an

animal. These studies also revealed that after digit training there was an areal expansion of dual-response representations, that is, cortical sectors over which stimulation produced movements about two or more joints. Movement combinations that were used more frequently after training were selectively magnified in their cortical representations. This close correspondence between changes in behavioral performance and electrophysiologically defined motor representations indicates that a neurophysiological correlate of a motor skill resides in M1 for at least several days after acquisition. The finding that cocontracting muscles in the behavior come to be represented together in the cortex argues that, as in sensory cortices, temporal correlations drive emergent changes in distributed motor cortex representations.

Key words: motor cortex; primates; squirrel monkey; motor learning; plasticity; hand

Numerous studies conducted primarily in somatosensory cortical areas over the past several years have revealed that representational maps (i.e., somatotopic maps of the body surface) are altered by manipulations of their sensory inputs (for reviews, see Merzenich et al., 1988; Kaas, 1991) (see also Kalaska and Pomeranz, 1979; Kelehan et al., 1981; Rasmusson, 1982; Kaas et al., 1983; Merzenich et al., 1983a,b, 1984; Rasmusson and Turnbull, 1983; Kelehan and Doetsch, 1984; Simons et al., 1984; Rasmusson et al., 1985; Wall and Kaas, 1986; Calford and Tweedale, 1988, 1991; Wall, 1988; Welker et al., 1989; Recanzone et al., 1990). Each manipulation resulted in substantial alterations in functional topography of somatosensory cortical areas. Although plastic changes in the cerebral cortex have been known for some time to occur developmentally, these studies demonstrating reorganization in *adult* primates indicate that cortical maps are alterable throughout life.

Although these studies demonstrate that reorganization in somatosensory cortex can be induced by pathological disturbances, more recent experiments show that sensory cortex is selectively altered by the behavioral experiences of intact animals. For ex-

ample, in adult owl monkeys, with behaviorally controlled tactile stimulation of one or two digit tips, the sensory representation of the stimulated skin surface in area 3b enlarged, and engaged skin surfaces were represented in correspondingly finer grain (Jenkins et al., 1990). Similarly, after a frequency discrimination task, the topographies of the representations of the trained hand were more spatially complex and changes in distributed responses were strongly correlated with behaviorally documented performance gains. These studies have revealed that the details of representation of the body surface in somatosensory cortical areas reflect the recent behavioral experiences of the animal under study (Recanzone et al., 1992b).

Evidence is also accumulating that indicates that *motor* cortex is similarly remodeled throughout life. For example, experiments conducted by Donoghue and colleagues have shown that cortical motor representations can be rapidly altered by peripheral nerve lesions in both developing and adult rats (Donoghue and Sanes, 1987; Sanes et al., 1990). Also, our own studies have shown that repetitive electrical stimulation of motor cortex, even at levels well below movement thresholds, induces changes in movement representations (Nudo et al., 1990) (see also Graham-Brown and Sherrington, 1912; Leyton and Sherrington, 1917). Local injection of bicuculline results in a rapid induction of changes in cortical motor topography in adult rats (Jacobs and Donoghue, 1991). Taken together, these studies indicate that the functional organization of motor cortex, like that of somatosensory cortex, is modifiable and selectively alterable throughout life.

If the functional organization of “movement representations”

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in the motor cortex can be altered by these peripheral and central manipulations, it is likely that, normally, experiential manipulations continually reshape the details of functional topography in the motor cortex, as in SI somatosensory cortical areas. The role of motor cortex in the acquisition of motor skills rarely has been addressed in this way. Modern studies of the role of motor cortex in motor control have used highly trained (usually overtrained), awake, behaving animals, and neurophysiological data have been derived in nearly every experiment only after the animal has reached performance criteria for the behavior (Evarts et al., 1983). Because somatosensory experiments indicate that training results in substantial modification of cortical maps, important interactions between behavioral performance and cortical physiology could be occurring in the motor cortex before these neurophysiological studies are initiated.

In the present experiment in adult squirrel monkeys, we tracked the topographies of distal forelimb representations in the primary motor cortical field (M1 or area 4), before and after behavioral training for a task that required the skilled use of the hand digits. The results show that motor cortex, like somatosensory cortex, is dynamically altered by behavioral experience. Several-fold increases in the complexity and in the cortical areas dedicated to the representations of specific movements and movement combinations that are important for the learned motor skill were recorded in these trained monkeys. At the end of a training epoch, M1 representations clearly were adapted specifically to selectively represent key aspects of the newly acquired skill.

MATERIALS AND METHODS

Sixteen detailed electrophysiological mapping studies were conducted in six adult male squirrel monkeys (*Saimiri boliviensis peruviansis*). Monkeys were young adults between 2 and 5 years of age. Each was free of any obvious physical or neurological deficits, and each was judged to be healthy before and after behavioral training and electrophysiological mapping sessions.

The general procedures were as follows. First, limited hand preference testing was conducted to determine each animal's hand preference for retrieval of small food pellets (see below). Several weeks to months later, an electrophysiological map of the distal forelimb representation was derived within M1 in the hemisphere contralateral to the preferred hand. Each animal was then randomly assigned to one of two groups: (1) a behavioral training group ($n = 3$) that underwent daily training on a pellet retrieval task ("digit-training task"); or (2) a control group ($n = 3$) that underwent no specific behavioral training. In each animal, after behavioral training (training group) or an equivalent period without training (control group), identical electrophysiological mapping procedures were repeated. Finally, after the two control procedures, one monkey in the control group underwent daily training at a key (eyebolt)-turning task ("forearm-training task") followed by a final electrophysiological mapping procedure.

Hand preference testing procedure

Hand preference testing was conducted using a modified "Klüver board" (Glees, 1961; Lawrence and Kuypers, 1968) following procedures described in detail previously (Nudo et al., 1992). This device consisted of a rectangular Plexiglas board, $24 \times 7.6 \times 1.8$ cm³ thick, containing four food wells of different diameters: 25, 19.5, 13, and 9.5 mm, or wells 1, 2, 3, and 4, respectively. The vertical sides of each of these wells were 5 mm high; the bottom of the wells tapered at a 30° angle to a central point.

Each animal was food-restricted for 18 hr before the hand preference testing procedure was conducted. Hand use preference was determined for 100 trials over a period of 2–3 d. In these tests, the Klüver board was attached to the front of the animal's home cage, ~12 inches above the height of the cage floor. The animal was required to support itself with one hand while reaching through the cage bars to retrieve pellets with the other. Each trial was recorded on videotape for later analysis. A single, banana-flavored, 45 mg food pellet (BioServe, Laurel, MD) was placed randomly into one of four wells, and the animal was allowed to retrieve it. If the pellet was not successfully retrieved within 1 min, it was removed

from the well and the next trial was begun. This time limit was imposed to minimize training effects. The videotape was reviewed later, and for each trial we recorded (1) the hand used on the initial reach for that trial, (2) the hand used on subsequent reaches, and (3) the hand used to dislodge or retrieve the pellet. Because these three measures were highly correlated, a "preference score" was derived for each animal that was equal to the average of the percentage of left-hand initial reaches and the percentage of left-hand retrievals for all wells.

Behavioral training procedures

Two types of behavioral training procedures were conducted: (1) a digit-training task using the same Klüver board used in hand preference testing; and (2) a forearm-training task using a rotatable eyebolt.

Digit-training task ($n = 3$). Each animal was trained in two separate 30 min sessions/d. Monkeys were food-restricted for 18 hr before each daily training session. All aspects of the training apparatus were identical to those used for hand preference testing. Training sessions consisted of alternating "priming periods" and "training periods." During each priming period, a single banana-flavored food pellet was placed in the largest (25 mm) well until retrieval. Pellets were then placed in consecutively smaller wells until retrieval. This sequence was repeated for the duration of the priming period (1 min). During a training period, a single pellet was placed in the smallest (9.5 mm) well until retrieval. Upon retrieval, another pellet was placed in the same well. This procedure continued until another priming period began (i.e., for 4 min) or until the end of the 30 min session. That is, during each priming period, retrieval from the smallest well was required on one of every four trials; during each training period, retrieval from the smallest well (9.5 mm) was required on every trial. Training continued for a minimum of 11 d and until the number of daily retrievals from the smallest (9.5 mm) well was ≥ 600 pellets for 2 consecutive days.

In one animal, a titration procedure was required to encourage efficient retrieval in a second training phase. This procedure was begun 3 months after phase I training and the subsequent mapping procedure. The titration procedure was conducted as follows. A fifth well was introduced that was intermediate in size between the 13- and 9.5-mm-diameter wells (wells 3 and 4, respectively). The diameter of this intermediate well was 11 mm (well 3.5). Titration training was conducted as in phase I but, instead of conducting intensive training on well 4, training was conducted initially on well 3. That is, during each training period, retrieval from well 3 (13 mm) was required on every trial. Daily training continued on well 3 until a criterion performance level was reached (2 of 3 d, >600 retrievals). The difficulty was then increased by introducing pellets into well 3.5 (11 mm) on 10% of the trials until criterion performance was reached. This difficulty level was followed by 75% well 3/25% well 3.5, then 50% well 3/50% well 3.5, then 25% well 3/75% well 3.5 and, finally, 100% well 3.5. The same procedure was used to progress eventually to criterion performance on well 4. The final criterion on well 4 (9.5 mm) was 3 consecutive days with >600 retrievals.

Videotapes were examined later frame-by-frame to assess the frequency of movements and movement combinations used in the task at each phase of training. Samples consisting of selected trials on the smallest well (well 4) were examined. For the duration of each trial, we identified and coded each distal forelimb movement and movement combination used until retrieval of the pellet was achieved. Movement categories were identical to those used for describing movements evoked by intracortical microstimulation (see Electrophysiological mapping procedure below). Movement combinations were movements of multiple joints that occurred simultaneously. Discrete movement events were delineated by starts and stops in the animal's motion during any given trial. At each training phase, the frequency of each movement category and movement combination was tallied and expressed as a percentage of total movement events for that stage (see Table 3).

Forearm-training task ($n = 1$). In a fourth animal, a behavioral training procedure was used that required repetitive cycles of supination and pronation of the forearm. The apparatus consisted of a rotatable eyebolt with an eye that was 1 inch in diameter. A metal rod was attached perpendicular to the axis of the eyebolt. As the eyebolt was rotated, the rod depressed one of two microswitches. The microswitches were arranged so that the maximum rotation of the eyebolt could be adjusted from a minimum of 20° to a maximum of 45°. The task required that the animal make alternating clockwise and counterclockwise rotations of the eyebolt to receive a banana-flavored pellet delivered from an automatic dispenser. The entire apparatus was mounted on the animal's home cage and was available to the animal 24 hr/d.

The rotation angle initially was set at 20°, and the animal was rewarded on a 100% reinforcement schedule, that is, each time either microswitch was activated was whenever a supination or pronation of the forearm was made. When a criterion performance of 1000 pellets/d was reached, the animal was required to alternate activation of the two microswitches, that is, to alternate supination and pronation. When criterion performance on this task was reached, the rotation angle was increased in two steps, from 20° to 32.5° to 45°. Once criterion performance was reached at the 45° rotation angle, a Plexiglas cylinder with an inside diameter of 1.5 inches was extended gradually over the eyebolt. This encouraged the use of one hand. The cylinder was extended in five steps to a distance just proximal to the elbow, to encourage forearm supinations and pronations while discouraging elbow flexion and elbow extension as well as lateral and medial rotation of the shoulder. When criterion performance was reached, an annulus was inserted into the end of the cylinder to further restrict movements of the proximal limb and shoulder. Once this task was performed proficiently, the schedule of reinforcement was reduced gradually to 5%. Final criterion performance was achieved when the animal performed at least 10,000 forearm pronations and supinations on each of 2 consecutive days.

Control group ($n = 3$). Three animals served as controls. In each animal, an electrophysiological mapping procedure was conducted. The animal was then placed back into its home cage. After a period of 1–2 months, a second, equally detailed electrophysiological mapping procedure was conducted.

Electrophysiological mapping procedure

Each animal was anesthetized initially with ketamine hydrochloride (20 mg/kg, i.m.). After tracheal intubation, the animal was administered halothane (1–2%) and nitrous oxide (75%) and placed in a stereotaxic frame. Core temperature was measured using a rectal probe; a homeothermic blanket maintained body temperature within 36.5–38.0°C throughout the experiment (typically 15–19 hr). Heart and respiration rates were monitored periodically. An indwelling cannula was inserted into the saphenous vein for delivery of intravenous fluids. Mannitol (8 cc/kg, 250 mg/cc) was administered slowly to reduce the likelihood of brain edema. Antibiotics (Crysticillin, ~60,000 U) were administered before surgery and every 12 hr thereafter during the procedure. Under sterile conditions, a limited craniotomy (~1.5 cm diameter) was made over M1. A small, plastic chamber was affixed with dental acrylic to the skull around the opening. After reflection of the dura, the chamber was filled with silicone oil (30k Centistoke, dimethylpolysiloxane, Dow 200 fluid).

The halothane and nitrous oxide were then withdrawn, and the animal was administered ketamine hydrochloride (diluted to 20 mg/cc with saline) intravenously at the rate of 15 mg/kg/hr. In addition, acepromazine (diluted to 0.1 mg/cc with saline) was administered as needed to control excessive muscle tone (typically 0.01 mg/kg per dose). The rate of continuous ketamine infusion was adjusted as needed to maintain a stable anesthetic state. Intracortical microstimulation (ICMS) mapping was conducted only during periods of stable anesthesia; it was halted during occasional periods of more shallow anesthesia marked by excessive muscle tone in forelimb muscles combined with rapid heart rate, or during occasional periods of deeper anesthesia marked by unusually high ICMS thresholds.

A magnified photograph of the cortical surface vasculature was obtained using a video frame-grabber. Stimulating microelectrodes consisted of glass micropipettes with 15–20 μm tip diameters. Micropipettes were <100 μm 2 mm from the tip and beveled to a sharp point. They were filled with 3.5 M NaCl. Impedances ranged from 750 k Ω to 1 M Ω . Microelectrodes were introduced on a fine grid pattern (250 μm interpenetration distances) sited with reference to the surface vasculature (see Fig. 3). At each electrode penetration site, conventional ICMS techniques were used to define evocable movements. Briefly, the micropipette was advanced perpendicular to the cortical surface to a depth of 1700–1800 μm using a hydraulic microdrive. Our previous data, as well as previously published data by others (Strick and Preston, 1982a; Gould et al., 1986; Nudo et al., 1992), have shown that thresholds for evoking movements are the lowest in this layer 5 depth range. Significant dimpling of the cortical surface rarely occurred using beveled pipettes. However, when dimpling was observed the cortex was allowed to return to its original position before stimulation. The stimulus consisted of a 40-msec-current train of thirteen 200- μsec -long monophasic cathodal pulses delivered at 350 pulses/sec from an electrically isolated, charge-balanced (capacitively coupled) stimulation circuit. Trains were delivered at a rate of 1/sec.

Current was monitored by observing the voltage drop across a 10 k Ω resistor in series with the stimulation circuit.

In the derivation of all maps, animals were maintained in a standard prone position. The contralateral forelimb was supported below the elbow in the same slightly flexed position throughout each experiment. The forelimb was manipulated only when necessary to stabilize the wrist to distinguish between wrist extension and digit extension.

At each site, the movement evoked by stimulation at near-threshold current levels was determined by the following procedure. Current was increased gradually from zero until a response was just visible. When the evoked movement was defined, the current was decreased until the movement disappeared and then was increased again gradually to find the current level required for evoking the movement with at least 50% of the train bursts. This current was defined as the “threshold current.” In each experiment, in a sample of ~10% of electrode penetration sites, a second observer independently determined the responses and threshold currents. If a response was not evoked at 30 μA , stimulation was halted and the site was designated as “nonresponsive.” A second movement was sometimes evoked reliably at or near threshold current levels. If a second movement was evoked consistently at ≤ 2 μA above the threshold intensity, the movements were defined as unresolvable and that cortical location was designated as a “dual-response” site. At some sites, the movement and threshold evoked by stimulation were recorded at a range of depths from 1400 to 2000 μm . This test was performed to ensure that the electrode was perpendicular to the cortical surface and that the lowest possible current thresholds were obtained.

The territorial extent of the area 4 distal forelimb representation was explored as completely as possible by using the following criteria. Penetrations were made at each coordinate of a 250 μm grid pattern until the distal forelimb area was circumscribed by sites evoking either proximal movements or no visible response. Small, minimal deviations were made in the 250 μm grids to avoid direct damage to surface arteries or veins. When nonresponsive sites were encountered, their response to stimulation was verified later in the same mapping procedure. To verify further that the entire distal forelimb area was explored completely, a number of selected outlying sites were examined that completely flanked the distal forelimb border (see Fig. 4).

Movements were described using conventional terminology as in previous papers (Gould et al., 1986; Nudo et al., 1992). For clarity, common terminology is used where appropriate. For example, digit 1 movements are called “thumb” movements, and digits 2–5 movements are called “finger” movements.

After mapping was completed, the plastic chamber was removed, the dura was replaced with gelfilm, the bone flap was reattached with stainless steel sutures or dental acrylic, the skin was sutured, and the wound was dressed with an antibacterial agent. The animal was monitored closely until it was alert (1–2 hr), and then the animal was transferred to a temperature-controlled incubator for complete recovery.

An identical electrophysiological mapping procedure was repeated several weeks or months later after behavioral training or a control period. In our hands, repeated mapping can be performed on the same animal at least four or five times without any untoward effects such as deterioration of stimulus-evoked responses or histological signs of unintended injury. However, a thin meningeal layer often forms in the weeks or months after the initial procedure, and extra care must be taken to remove this tissue during subsequent procedures.

Calculation of areal extent of movement representations

To define unambiguous boundaries between different movement regions and thus derive reliable areal measurements, we used a computer algorithm that delineated discrete regions encompassing sites at which stimulation evoked similar movements (for further details, see Nudo et al., 1992). Using an image analysis program (IMAGE, v1.45), the total areal extents of each movement category were derived. Finally, for each movement category, threshold current levels were tallied and analyzed.

For each animal, the areal extent of each movement category was compared for differences between pre- and post-training maps in the training group or for differences in the two sequential maps in the control group. In addition, the mean threshold current for each movement category was compared for differences in sequential maps.

Histological analysis

After completion of these experiments, boundaries of the distal forelimb representations were marked either by small, electrolytic lesions or by injection of fluorescent latex microspheres. The animal was then injected

with a lethal dose of pentobarbital (100 mg/kg) and perfused: first with 0.9% saline, 0.2% lidocaine hydrochloride, and 1% heparin; then with 10% formalin. The brain was removed subsequently and immersed in 30% sucrose for 1–2 d. It was cut in 50 μ m frontal sections. Every other section was mounted and stained with cresyl violet for cytoarchitectonic analysis. This sampling frequency was sufficient to locate each penetration site indicating the boundaries of the distal forelimb representation (electrolytic lesions or fluorescent microspheres). Tracks produced by the fine, beveled glass micropipettes used for recording stimulus-evoked movements in these studies were not detectable using these techniques.

RESULTS

Behavioral results

Three squirrel monkeys were trained to retrieve banana-flavored pellets from four food wells graded in diameter from 25 to 9.5 mm as outlined in Materials and Methods. On the basis of daily frame-by-frame analysis of videotapes, behavioral performance was tracked by measuring (1) the number of pellets retrieved and (2) the number of finger flexions per retrieval. Although the number of finger flexions was recorded because this movement was easy to identify on videotapes, it should be noted that each unsuccessful finger flexion consisted of a finger flexion/finger extension pair.

On the first day of training, each of the three animals readily retrieved pellets from the three largest wells. Each animal made repeated attempts (finger flexions and extensions) to retrieve pellets from the smallest well (9.5 mm diameter), with varying degrees of success. In two of the three animals, performance improved rapidly on the smallest well over the course of a few days of intensive training, so that criterion performance (2 consecutive days with ≥ 600 daily retrievals) was met by day 11. Over the course of the 11 training days, the total number of daily retrievals increased, whereas the number of finger flexions per retrieval decreased (Fig. 1A). The total number of daily retrievals was significantly and negatively correlated with the number of finger flexions per retrieval ($r = -0.787$, $p = 0.004$).

In the third case (#1598), criterion performance was not achieved by the end of 11 d of training. A mapping procedure was conducted after this animal's 11 d of subcriterion performance and will be presented below. After this second mapping procedure, a titration procedure was used to shape this animal's performance gradually on the smallest well. Using the titration procedure, criterion performance was achieved after an additional 39 d for a total training period of 50 d. The number of finger flexions per retrieval for each of the three animals on days 1, 11, and 50 (case #1598 only) is shown in Figure 1B.

In addition to the improvement in performance, movements became progressively more stereotypic during the course of training. By the final day of training at criterion performance levels, each of the three animals routinely retrieved pellets from the smallest well using the same movement sequence (Fig. 2). First, the pronated distal forelimb extended through the cage bars toward the target well. Second, the fingers extended and inserted into the well (typically digits 2 and/or 3; Fig. 2A). Third, the fingers flexed within the well and then stopped (Fig. 2B). Fourth, the fingers flexed a second time, and then the wrist gradually extended (Fig. 2C,D). The pellet typically was lodged between phalangeal (glabrous) surfaces of digits 2 and/or 3 and the interdigital pads (pads 2 and/or 3). Fifth, the wrist continued to extend as a discrete movement. Sixth, as the pellet was retrieved from the well, the forearm was gradually supinated (Fig. 2E). Finally, the distal forelimb was retracted back through the cage bars. In a later section, these movements and movement combinations used in

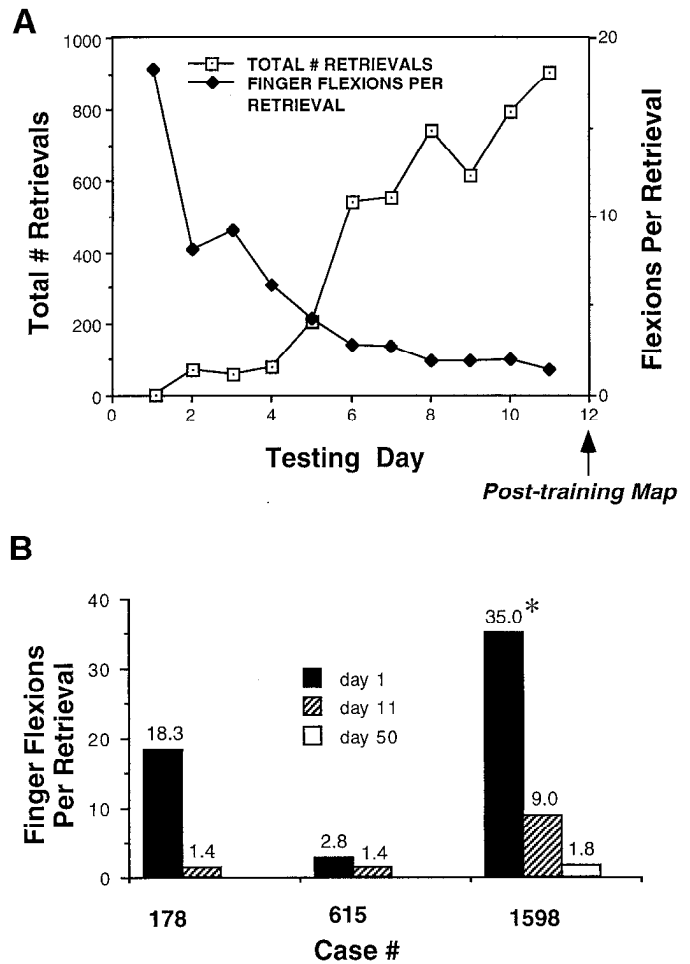


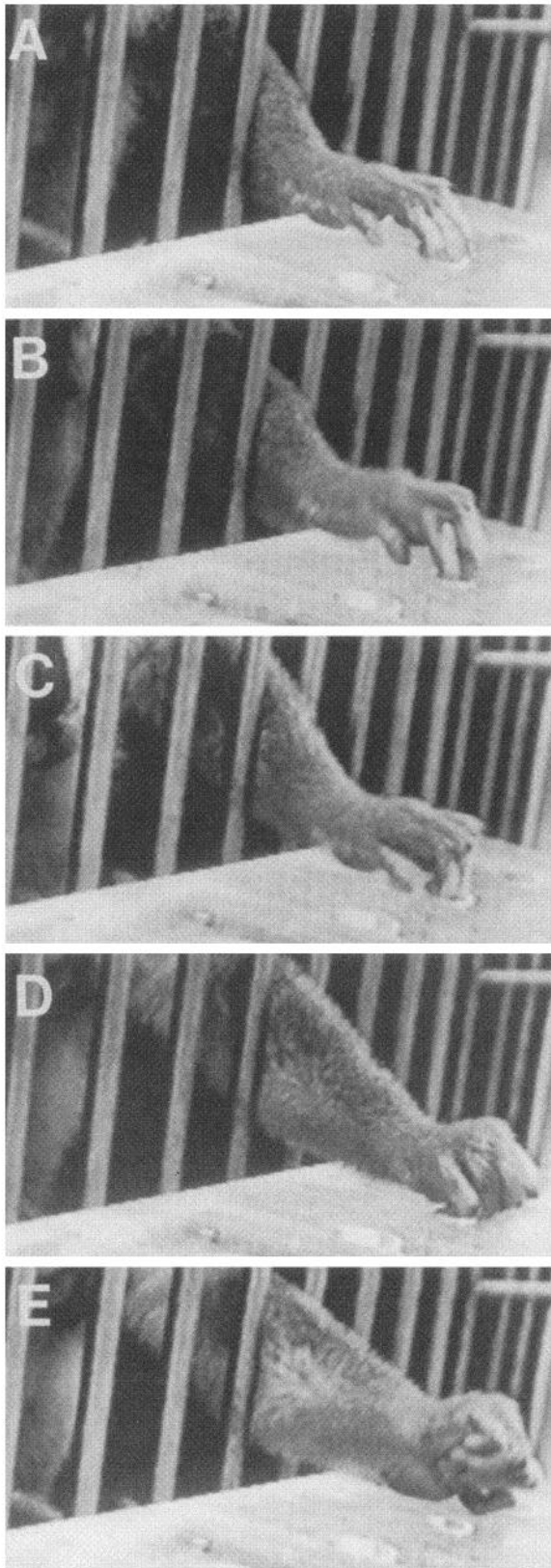
Figure 1. Performance on a Klüver board. *A*, Total number of successful retrievals per day (open squares) and average number of finger flexions per retrieval (solid diamonds) for case #178. This rapid acquisition was similar for case #615. Case #1598 required a titration procedure to ultimately achieve performance criterion. *B*, Average number of finger flexions per retrieval on the first and last days of training for each of the three animals. Asterisk indicates that data are compiled from the first two training days, because case #1598 made no successful retrievals on the first day of training.

the task are compared with changes in movement representations after training.

It is important to note that squirrel monkeys do not exhibit functional opposition of the thumb and index finger, in contrast to many Old World primate species (Costello and Fragaszy, 1988). The pellet was withdrawn with a multidigit flexion, and prehension was achieved by the opposition of digits 2 and/or 3 with the interdigital pad. The thumb was either moved in concert with the other digits or was braced against the platform while the fingers flexed and extended. Contact between the thumb and the food pellet was rare.

Organization of distal forelimb representation

In general, the organization of the distal forelimb representation in M1 was as described in earlier reports in this species (Donoghue et al., 1992; Nudo et al., 1992). The caudal boundary was located ~ 1 – 2 mm rostral to the central sulcus, near its lateral edge (Figs. 3, 4). The distal forelimb representation was bounded medially, rostrally, and laterally by more proximal movement representations (primarily elbow and shoulder) and caudally by a



Finger Extension

Finger Flexion

**Finger Flexion +
Wrist Extension**

Wrist Extension

Forearm Supination

Figure 2. Sequence of photographs showing movements used to retrieve a pellet from a 9.5 mm well (well 4) of a Klüver board. *A*, The fingers extended as the arm moved toward the well. *B*, The fingers flexed within the well and then stopped. *C*, A second finger flexion occurred, but before the finger flexion movement was completed the wrist extended. *D*, The wrist continued to extend as a discrete movement and then stopped when the wrist was fully extended. *E*, As the pellet was retrieved from the well, the forearm gradually supinated.

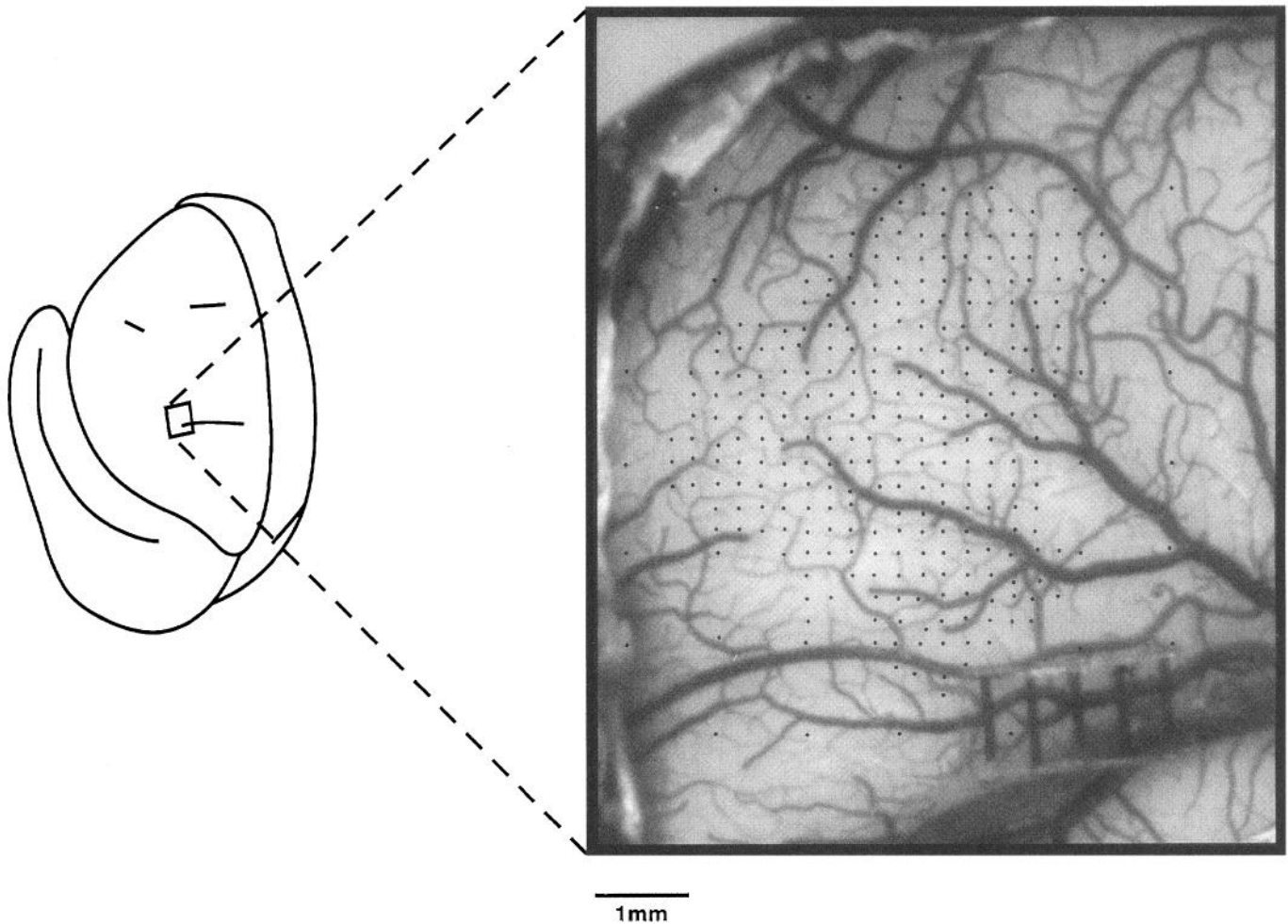


Figure 3. ICMS techniques used to derive the representation of distal forelimb movements in M1 of squirrel monkey. *Left*, Dorsolateral view of squirrel monkey neocortex (left hemisphere), outlining the cortical territory explored in a typical motor-mapping procedure. *Right*, Enlarged video image of cortical surface in case #1603 showing blood vessels used as landmarks for microelectrode insertion. Microelectrode penetration sites are indicated by small black dots.

nonresponsive zone (i.e., no movements evoked by currents $\leq 30 \mu\text{A}$). Although the forelimb representation was usually a single contiguous sector, it could be divided occasionally into two sectors by more proximal (elbow and shoulder) representations.

Because the forelimb representation was reasonably well circumscribed on three sides by more proximal movement representations and on the remaining (caudolateral) side by an unresponsive region, the entire representation was delineated and explored in detail. Although $>99\%$ of the sites at which stimulation evoked movements at low current levels ($\leq 30 \mu\text{A}$) were found to be located within cytoarchitectonic area 4 (Nudo et al., 1992), a few responsive sites were identified subsequently on histological grounds as being within cortical area 3a. Data from sites that were determined unambiguously to be within area 3a (i.e., $\geq 500 \mu\text{m}$ from the area 3a/4 border) were eliminated from statistical analyses. The mean number of penetrations required to explore the entire forelimb representation on this $250 \mu\text{m}$ sampling grain was 312.6.

The total areal extent of distal forelimb movement maps was examined at each of four hierarchical levels of specificity, as described in a previous paper (Nudo et al., 1992). For example, distal forelimb (level 1) was divided into digit and wrist/forearm categories (level 2), digit was divided further into finger and

thumb categories (level 3), and finger was divided still further into finger flexion, finger extension, finger abduction, and finger adduction categories (level 4). In addition to these single-movement categories, we also examined so-called dual-response movement categories; that is, at threshold current levels ($\pm 2 \mu\text{A}$), ICMS sometimes evoked two different movements such as finger flexion and wrist extension. Each dual-response combination was treated as a separate movement category.

Finally, we examined various combinations of these mutually exclusive categories, such as the category including all digit movements, either alone or in combination with other responses. These combined categories are referred to hereafter as inclusive categories. For example, the inclusive digit area includes the digit area, the digit + wrist/forearm area, and the digit + proximal area. For each movement category at each hierarchical level, we defined total representational area and percentage of total distal forelimb area (relative area). Thus, area measurements were performed for movement categories at hierarchy level 1 (i.e., distal forelimb), level 2 (i.e., digit, wrist/forearm), level 3 (i.e., finger, thumb, etc.), and level 4 (i.e., finger flexion, finger extension, finger abduction, etc.).

The distal forelimb area was highly variable in extent among individual animals. The mean areal extent for the 12 maps in six

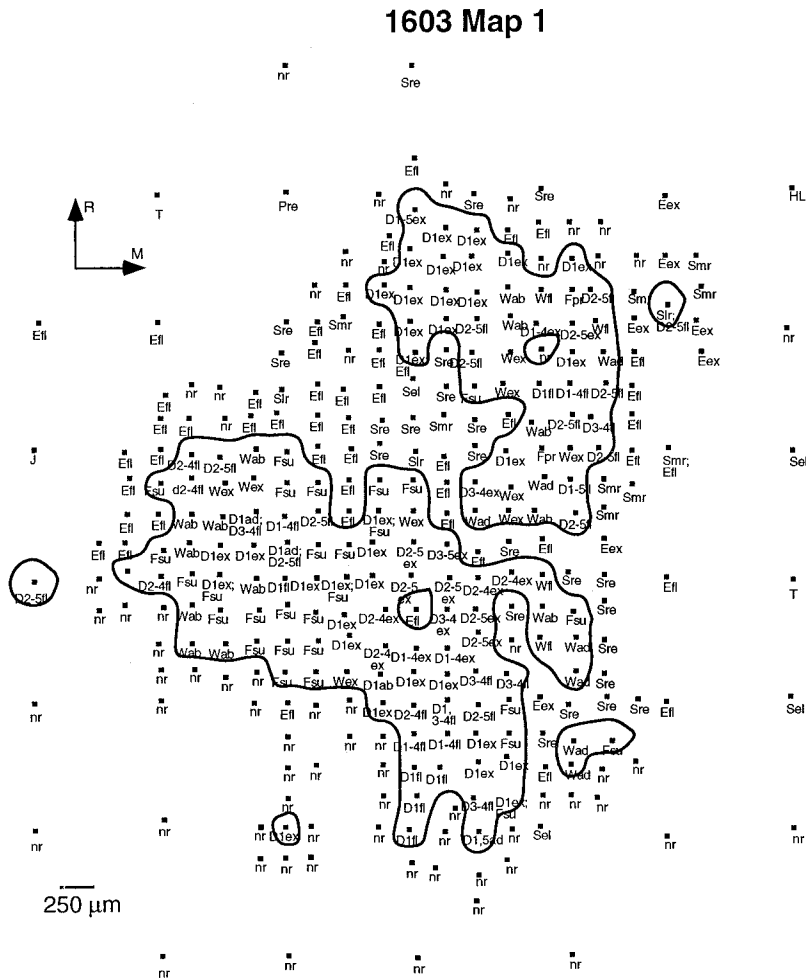


Figure 4. Movements evoked at near-threshold current levels from each of the 313 sites shown in Figure 3. The distal forelimb is outlined to illustrate its total areal extent within M1. Abbreviations: *D*, Digit; *W*, wrist; *F*, forearm; *S*, shoulder; *E*, elbow; *P*, pinna; *J*, jaw; *T*, trunk; *HL*, hindlimb; *nr*, no response; *fl*, flexion; *ex*, extension; *ad*, adduction; *ab*, abduction; *mr*, medial rotation; *lr*, lateral rotation; *su*, supination; *pr*, pronation; *el*, elevation; *re*, retraction; *M*, medial; *R*, rostral. Numbers indicate specific digits involved in movement.

individual animals was 12.08 mm² and ranged from 7.47 to 14.46 mm² (Table 1). As reported in a previous paper (Nudo et al., 1992), no significant correlation was found between distal forelimb representational area and body weight ($r = 0.144, p = 0.79$ for animals reported in the present study).

The representational area for movement classes in hierarchical levels 2–4 was also highly variable. For example, the digit area averaged 6.37 mm² among the 12 representational maps, ranging from 2.74 to 9.28 mm². On average, the digit area accounted for 52.2% of the total distal forelimb representation. The wrist/forearm area averaged 4.66 mm² and ranged from 2.46 to 6.71 mm². On average, the wrist/forearm area accounted for 38.6% of the total distal forelimb representation. The digit + wrist/forearm dual-response area averaged 0.65 mm² and ranged from 0.05 to 1.56 mm². On average, the digit + wrist/forearm area accounted for 5.6% of the total distal forelimb area (Table 1).

Relative stability of movement representations in control cases

Movement representations were not identical between mapping procedures in control cases (Fig. 5). Considerable site-by-site variation was evident throughout the distal representation. However, in general, the topography of distal forelimb representation remained relatively constant. With respect to the surface vasculature, the distal forelimb representation was confined to the same cortical territory in both maps. Also, the general locations of mosaical clusters of movement categories were similar in the two

maps. Still further, the total distal forelimb representation was relatively constant. Finally, very little change was evident in the percentage of total area occupied by each movement category. In the present sample, the variability between animals appeared to be much greater than the variability between mapping procedures of the same animal (see Fig. 5). No systematic areal changes were apparent.

Changes in movement representations after digit training

Initial examination of distal forelimb representations derived in pre- and post-training maps revealed several apparent changes in movement topography. For example, expressed as a percentage of total distal forelimb area, the digit area increased in two of three cases, whereas the wrist/forearm area decreased in each of the cases (Fig. 6). Thus, despite the mosaical representation of distal forelimb movements and the large variability across individuals in representational area, it appears that systematic changes in individual movement representations occur in M1 after motor training.

To determine whether apparent changes between pre- and post-training representational maps were significantly different from control procedures, each of the mutually exclusive movement categories listed in Table 1, as well as various combinations of these movement categories, was submitted to statistical analyses. Movement categories for which total areal representation was <2% of the total distal forelimb area in the 12 maps were

Table 1. Mean area and percent of total distal forelimb area for various movement classes

Movement	Area (mm ²)	SD	% Total	SD
Distal forelimb	12.08	2.43	100.00	—
Digit	6.37	1.95	52.18	11.50
Wrist/forearm	4.66	1.45	38.60	8.89
Digit + wrist/forearm	0.65	0.48	5.60	4.32
Digit + proximal	0.23	0.28	2.09	2.74
Wrist/forearm + prox.	0.18	0.23	1.53	1.72
Fingers	4.48	1.17	36.99	5.76
Thumb	1.89	1.11	15.15	8.82
Wrist	3.36	1.21	27.77	7.46
Forearm	1.30	0.49	10.84	3.93
Finger + wrist	0.37	0.36	3.24	3.16
Finger + forearm	0.01	0.03	0.13	0.36
Finger + proximal	0.14	0.20	1.40	2.43
Thumb + wrist	0.08	0.09	0.70	0.85
Thumb + forearm	0.20	0.20	1.64	1.49
Thumb + proximal	0.09	0.13	0.70	1.02
Wrist + proximal	0.11	0.16	0.95	1.17
Forearm + proximal	0.09	0.19	0.72	1.37
Finger flexion	2.06	0.50	18.28	7.79
Finger extension	2.08	1.51	16.23	11.40
Finger abd./add.	0.34	0.53	2.49	3.74
Thumb flexion	0.44	0.43	3.55	3.22
Thumb extension	1.23	0.65	9.91	5.52
Thumb abd./add.	0.21	0.24	1.69	1.91
Wrist flexion	0.17	0.23	7.01	4.57
Wrist extension	1.78	0.99	15.25	8.65
Wrist adduction	0.98	0.87	7.58	5.80
Wrist abduction	0.44	0.35	3.60	3.06
Forearm pronation	0.38	0.27	3.12	2.29
Forearm supination	0.91	0.40	7.67	3.57
Fing. flexion + w.ext.	0.24	0.25	2.24	2.65
Thumb fl. + w.ext.	0.03	0.06	0.27	0.45
Thumb ext. + fa.sup.	0.14	0.17	1.20	1.38
Other finger (dual)	0.22	0.23	1.71	2.37
Other thumb (dual)	0.26	0.52	2.16	4.56
Other wrist (dual)	0.33	0.64	2.61	4.42
Other forearm (dual)	0.23	0.23	1.96	1.83

Abbreviations: prox., Proximal; abd., abduction; add., adduction; w.ext., wrist extension; fl., flexion; ext., extension; fa.sup., forearm supination.

eliminated from further analysis. Thus, the total number of movement categories submitted for statistical analysis was 57. Repeated-measures ANOVA was used to test differences between representational areas in the two maps as a function of treatment condition (training vs control conditions). When significant map × training condition interactions were found, paired comparisons (two-tailed *t* tests, *p* = 0.05) were used as post hoc tests to examine further the differences between pre- and post-training representational areas. To normalize percentage entries, arcsin transformations were used on these values before statistical testing (Zar, 1984).

When the entire distal forelimb representation was examined, representational area increased in each of the three training cases by an average of 0.48 mm², corresponding to an average percent-

age increase of 5.0% (3.9, 9.5, and 1.6% in cases 178, 615, and 1598, respectively). This increase was *not* significantly different from control (*p* < 0.05). However, when distal forelimb movements were subdivided (hierarchical levels 2–4 and their combinations), several significant differences were found between training and control procedures. Because the total distal forelimb area did not change significantly, statistical analyses are reported for relative representational areas expressed as a percentage of total distal forelimb area. Of the 57 movement categories examined, seven significant differences were found between pre- and post-training representational areas. Table 2 lists these statistically significant results as well as the results of three additional statistical tests that approached significance.

The areal extent of four single-movement representations differed significantly between training and control procedures. As shown in Table 2, the (inclusive) digit extension representation *increased* in relative area in training animals compared with controls. In contrast, the wrist, wrist abduction, and (inclusive) wrist abduction representations *decreased* in relative area in training animals compared with controls. In addition, increases in the (inclusive) finger representation and decreases in the (inclusive) wrist representation approached statistical significance.

The relative areal extent of two dual-response representations differed significantly between training and control procedures. The digit + wrist/forearm and finger flexion + wrist extension representations *increased* in areal extent in training animals. After training, the finger flexion + wrist extension representation increased nearly 2.5-fold from 0.12 to 0.41 mm², or from 1.6 to 4.2% of the total distal forelimb area. In addition, increases in the digit flexion + wrist extension representation approached statistical significance.

Neither the finger flexion nor the finger extension representations were significantly different between training and control procedures. However, when these representations were combined, the resulting finger flexion/extension representation increased in relative areal extent in training animals compared with controls. In training animals, the finger flexion/extension representation increased from 3.72 to 5.35 mm², a 44% increase, whereas in control animals this representation decreased from 4.28 to 3.97 mm², a 7% decrease. Expressed as a percentage of distal forelimb area, the finger flexion/extension representation increased significantly from 33.1 to 46.2% in training animals, whereas the representation remained relatively constant in controls (33.85–33.82%).

In summary, digit training resulted in statistically significant changes in the relative areal extent of several movement representations, including increases in digit extension, finger flexion + wrist extension, and finger flexion/extension representations and decreases in wrist abduction representations. Several of these significant changes are illustrated graphically in Figure 8. It should be noted that the absolute (as opposed to relative) areal extents of many of these same movement representations changed significantly but are not reported here.

Changes in movement thresholds after digit training

To determine whether any of the changes in representational area were related to changes in the thresholds for evoking movements, thresholds for each of the 57 movement categories were determined for each of the three training cases. Two movement categories showed significant *increases* in movement threshold. Thresholds for finger movements increased in each of the three training cases from an average of 12.94 to 15.46 μA (*t* = 6.46,

CONTROL CASES: DIGIT, WRIST/FOREARM REPRESENTATIONS

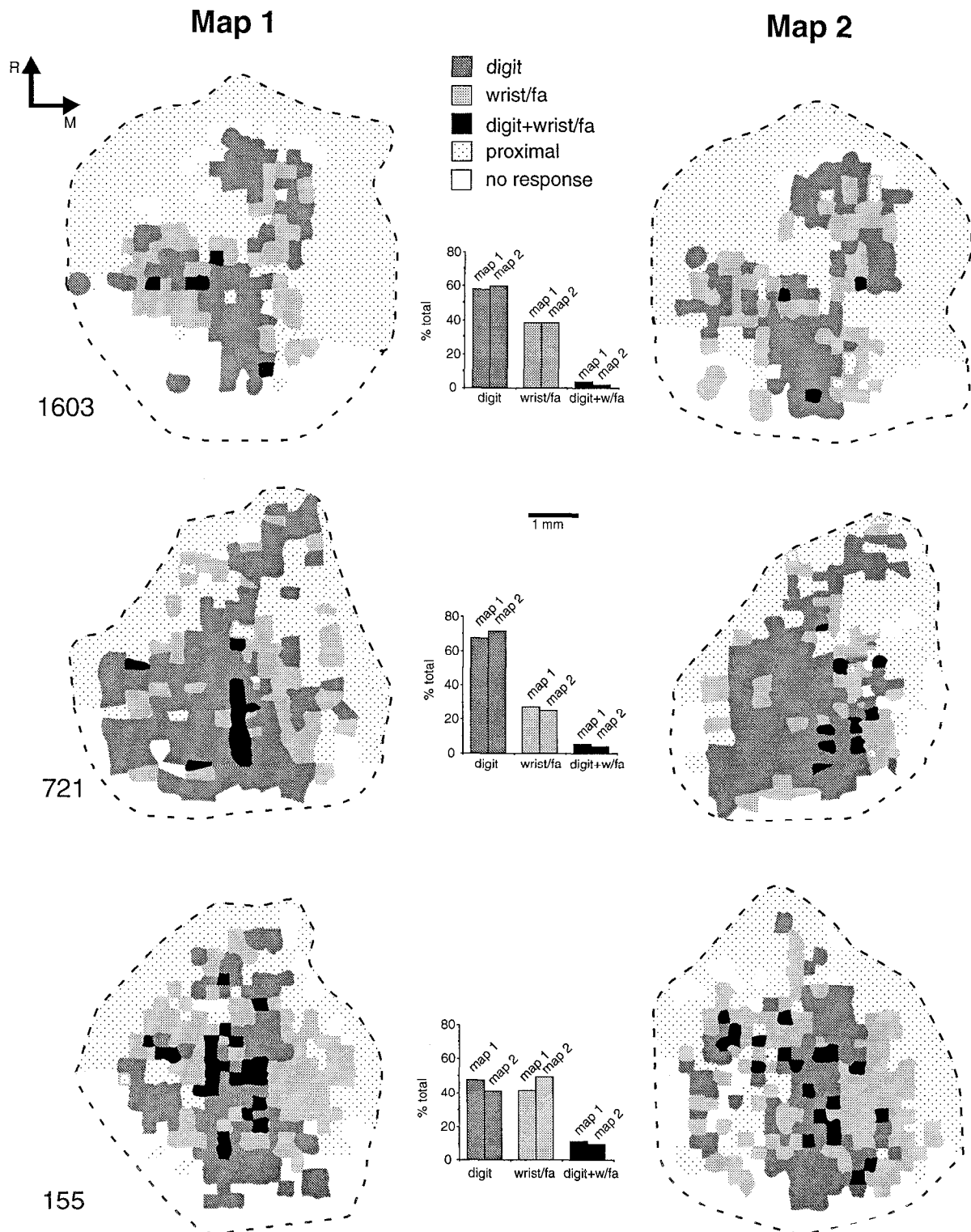


Figure 5. Representation of the distal forelimb in cortical area 4 derived from two separate mapping procedures in three control animals. In this illustration, distal forelimb movements have been broadly categorized as digit (dark gray), wrist/forearm (wrist/fa, light gray), digit + wrist/forearm (digit + w/fa, black), or proximal (stippled) movements. Nonresponsive areas are shown in white. For simplification, digit + proximal movements are included with digit; wrist/forearm + proximal movements are included with wrist/forearm. Dashed lines indicate extent of explored region. All maps are depicted in the left hemisphere.

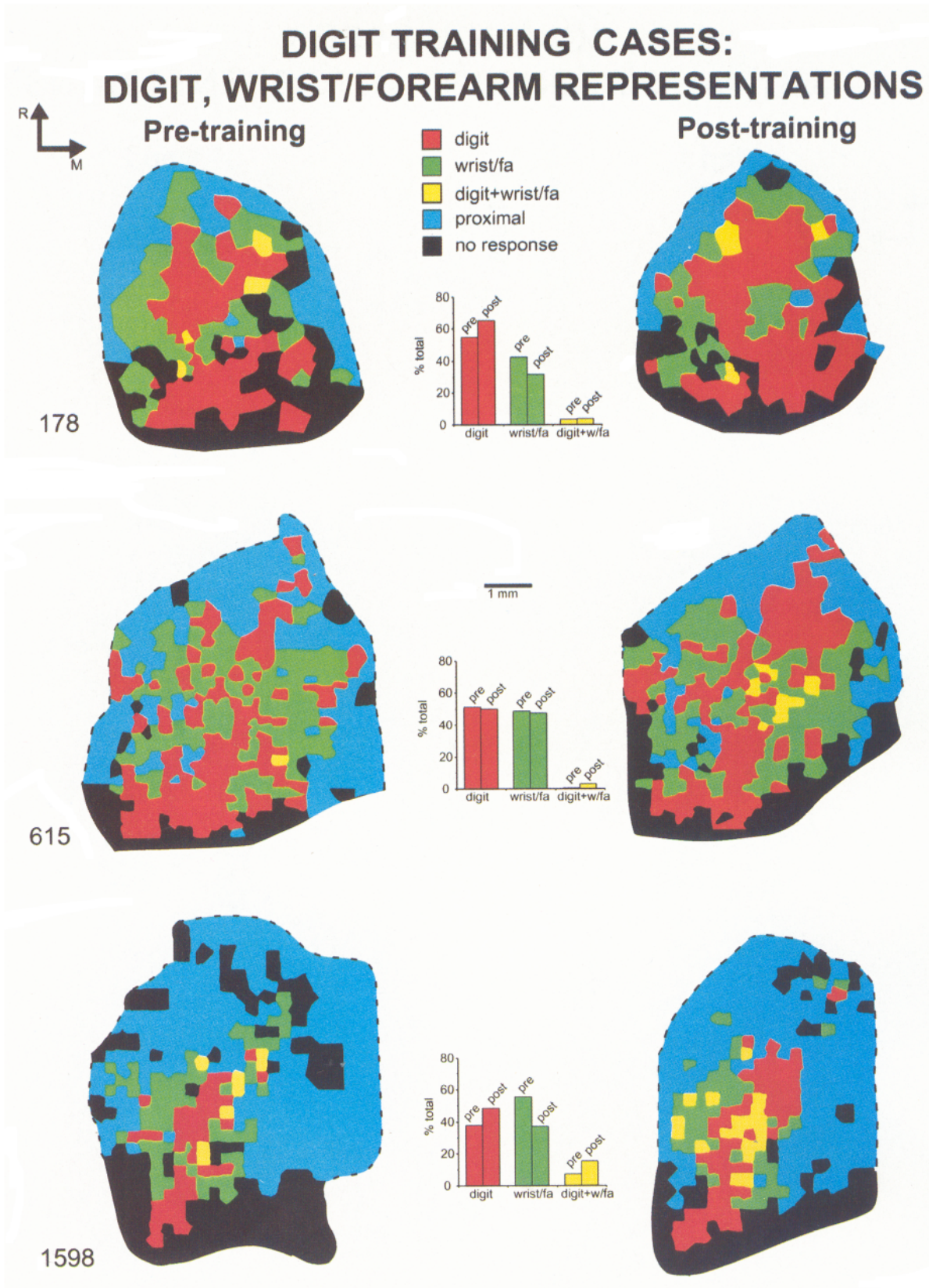


Figure 6. Representation of the distal forelimb in cortical area 4 derived from pre- and post-training mapping procedures in three training animals. In this illustration, distal forelimb movements have been broadly categorized as digit (red), wrist/forearm (green), digit + wrist/forearm (yellow), or proximal (blue) movements. Nonresponsive areas are shown in black. Abbreviations as in Figure 5.

DIGIT TRAINING CASES: FINGER EXTENSION, FINGER FLEXION, WRIST ABDUCTION REPRESENTATIONS

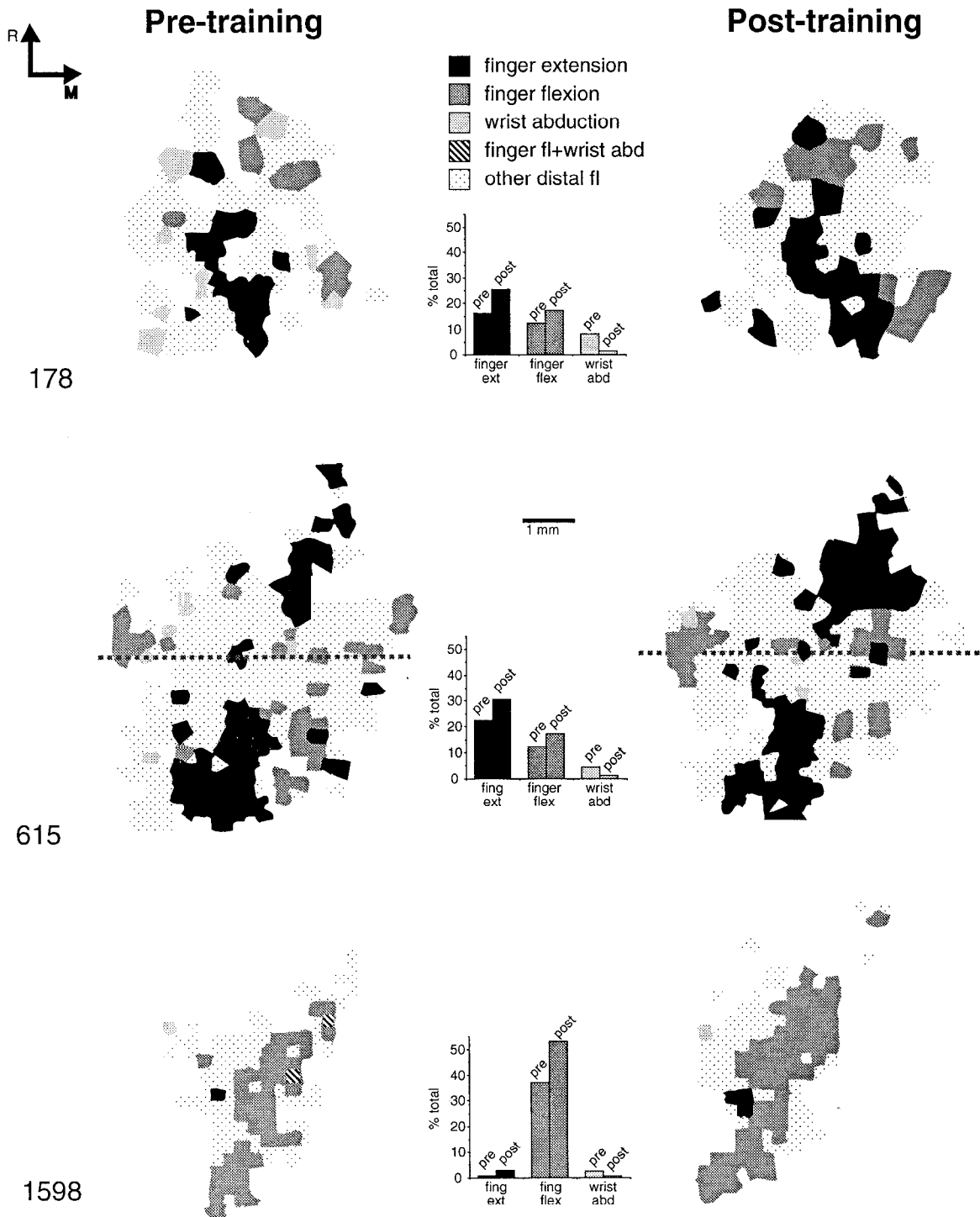


Figure 7. Representation of finger extension, finger flexion, and wrist abduction movements in cortical area 4 derived from pre- and post-training mapping procedures. In this illustration, finger extension movements are shown in *black*, thumb flexion movements are shown in *dark gray*, wrist abduction movements are shown in *light gray*, and finger flexion + wrist abduction movements are indicated by *diagonal lines*. For simplification, other dual-responses are included in single-movement categories. In *bar graphs*, finger flexion + wrist abduction dual-responses are included in each of the individual movement categories. Despite a large variation in movement representations among individuals, similar changes were evident in each of the three cases. That is, the relative area devoted to both finger extension and finger flexion movements increased in each of the three cases; the relative area devoted to wrist abduction movements decreased in each of the three cases. *Dotted line* in case #615 denotes division of distal forelimb representation into caudal and rostral sectors. *Dashed lines* indicating extent of explored region (Figs. 5, 6) have been eliminated in this and subsequent figures for clarity. *fl*, Flexion; *ext*, extension; *flex*, flexion; *abd*, abduction.

Table 2. Statistical results

Movement	ANOVA results ^a		% Distal forelimb area means \pm SD			
			Digit training group		Control group	
	F	P	Map 1	Map 2	Map 1	Map 2
Digit + wrist/forearm	9.95*	0.034	3.58 \pm 3.38	7.23 \pm 6.77	6.61 \pm 4.07	5.00 \pm 4.10
Wrist	10.14*	0.033	34.56 \pm 6.22	26.68 \pm 8.68	21.92 \pm 2.68	27.91 \pm 7.89
Finger (inclusive)	6.93	0.058	34.92 \pm 5.27	47.88 \pm 7.30	42.97 \pm 8.47	41.31 \pm 7.14
Wrist (inclusive)	6.17	0.068	37.63 \pm 8.91	32.94 \pm 9.15	26.66 \pm 6.15	33.29 \pm 9.61
Finger flexion + wrist extension	14.39*	0.019	1.55 \pm 2.38	4.21 \pm 4.10	2.49 \pm 2.37	0.71 \pm 0.61
Finger flexion/extension	8.25*	0.045	33.13 \pm 4.79	46.23 \pm 8.56	33.85 \pm 8.93	33.82 \pm 13.91
Digit extension (inclusive)	7.93*	0.048	22.81 \pm 16.86	27.04 \pm 17.49	37.23 \pm 7.01	35.96 \pm 6.60
Digit flexion + wrist extension	7.28	0.054	1.55 \pm 2.38	4.94 \pm 4.20	2.49 \pm 2.37	1.06 \pm 0.43
Wrist abduction	19.25*	0.012	4.51 \pm 3.74	0.84 \pm 0.73	4.43 \pm 3.62	4.62 \pm 2.94
Wrist abduction (inclusive)	13.52*	0.021	5.04 \pm 2.98	1.09 \pm 0.31	4.55 \pm 3.55	4.62 \pm 2.94

^aANOVA (with repeated measures) was used to test differences between relative representational area in the two maps as a function of treatment condition (map X training condition interactions). Statistically significant *F*-values indicate that areal changes between Map 1 and Map 2 differ between training and control groups. *Significant differences at $p < 0.05$.

$p = 0.023$). Likewise, thresholds for finger extension movements increased in each of the three training cases from an average of 10.41 to 14.20 μ A ($t = 4.45$, $p = 0.047$); that is, more current was required to evoke finger and finger extension movements after training. No significant differences in threshold were found for any of the movement categories in control cases.

It is possible that some of the changes in representational area observed in these procedures were attributable to systematic changes in movement thresholds. For example, if more current was required to evoke finger extension movements after training, then an expanded finger extension representation may reflect the "unmasking" of a larger finger representation zone that was not seen because of our definition of movements at just-threshold current levels. To examine this possibility in more detail, in one case (#1598) at each site we recorded movements evoked at a fixed 20 μ A current level in addition to the threshold current. At threshold current levels, the finger extension area increased from 0.06 mm² before training to 0.24 mm² after training, a fourfold increase. At the fixed suprathreshold current level of 20 μ A, the finger extension area increased from 0.19 to 0.57 mm², a threefold

increase. Thus, even at fixed suprathreshold current intensities, the areal extent of finger extension representations increased.

The possibility that systematic changes in movement thresholds play a role in expanded representations of dual-response areas was also explored by examining fixed suprathreshold current responses. As shown in Figure 9, increasing current from threshold levels to 20 μ A resulted in a small increase in the areal representations of finger flexion and wrist extension. However, after training the areal extent of the finger flexion zone, but not the wrist extension zone, increased substantially. This was evident at both threshold and 20 μ A current levels. Perhaps surprisingly, the average current required to evoke finger flexion increased slightly, whereas the average current required to evoke wrist extension and finger flexion + wrist extension *decreased* substantially.

Rostral-caudal differences in use-dependent reorganization

Although changes in the topography of movement representations occurred throughout the distal forelimb field, it appeared that some changes were greater in the rostral sector of area 4. For

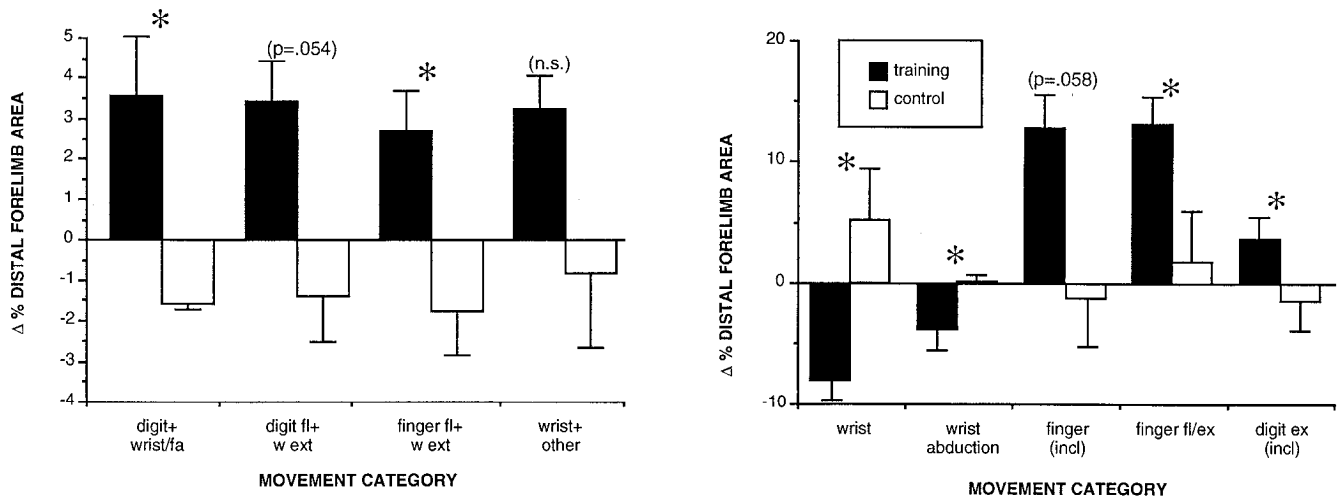


Figure 8. Changes in percentage of distal forelimb area devoted to various movement representations in M1 after digit-training and control procedures. Asterisks indicate statistically significant differences between training and control procedures using repeated-measures ANOVA ($p < 0.05$). *fa*, Forearm; *w ext*, wrist extension; *n.s.*, not significant; *incl*, inclusive; *fl*, flexion; *ex*, extension.

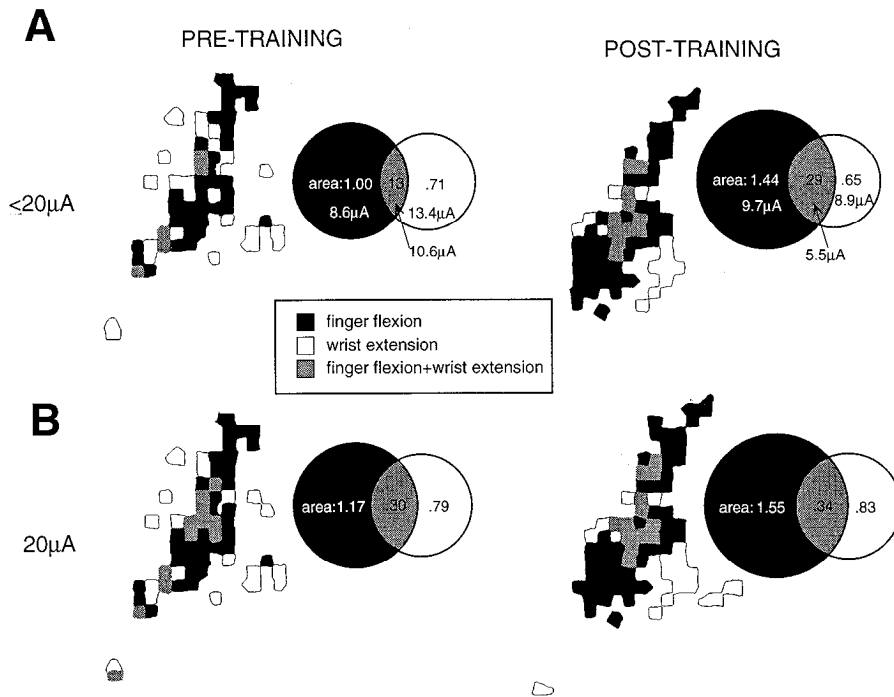


Figure 9. Representation of finger flexion and wrist extension in case #1598 at (A) threshold current levels and (B) a fixed current level of $20 \mu A$. In A, only sites at which threshold was $\le 20 \mu A$ were considered. Venn diagrams depict normalized areas and mean thresholds for each movement category. Finger flexion and wrist extension areas are inclusive. Increasing current from threshold levels to $20 \mu A$ resulted in a small increase in the areal representations of finger flexion and wrist extension. After training, the finger flexion zone as well as the finger flexion + wrist extension zone increased substantially in total areal extent. Training also resulted in a decrease in the average threshold for evoking wrist extension in this case (#1598). These results suggest that, after training, increased representational area for finger flexion + wrist extension occurs by (1) expansion of finger flexion representation into wrist extension and other territories and (2) decreased thresholds for wrist extension.

example, in case #615 a large, contiguous digit representation appeared in the rostral portion of the distal forelimb field after motor training (Figs. 6, 7). This enlarged representation appeared to invade the adjacent wrist/forearm and elbow/shoulder representations. To determine whether these apparent differences were statistically significant, the distal forelimb representation was subdivided into rostral and caudal halves. First, in each animal the rostral and caudal limit of the distal forelimb representation derived in the pretraining map was demarcated. A line was then drawn bisecting the distal forelimb representation into rostral and caudal halves. This line was then drawn over the post-training map at the same anatomical location with respect to the surface vasculature. Paired *t* tests were used as post hoc analyses to examine rostral-caudal differences.

Of the movement categories that were significantly or nearly significantly different between pre- and post-training maps (Table 2), two were significantly different in the rostral, but not the caudal, sector (Fig. 10). First, the relative finger flexion dual-response area (finger flexion + other) was larger in each of the three post-training maps in both rostral and caudal halves. However, this increase was significant only in the rostral half. Second, the relative wrist abduction area decreased in each of the three post-training maps in both the rostral and caudal halves. This decrease was significant only in the rostral half. In addition, the relative finger (inclusive) area increased in both the rostral and caudal halves. This decrease was significant only in the rostral half.

Progressive changes in motor representations during initial acquisition, extinction, and reacquisition of a skilled motor task

To determine the progression of changes in motor representations during the acquisition of a behavioral task and whether these changes are reversible, one animal underwent five complete mapping procedures spanning >500 d: (1) baseline map, (2) post-training phase I map (subcriterion performance), (3) post-training

phase II map (criterion performance), (4) postextinction map, and (5) post-reacquisition map.

Behavioral performance

Phase I training. Phase I training was conducted using the Klüver board for 11 d. This training procedure was identical to that described for cases #615 and #178. However, the behavioral performance of case #1598 at the end of the training phase was markedly lower. On day 11, cases #615 and #178 retrieved >600 pellets (criterion performance), whereas case #1598 retrieved only 85 pellets. Also, on day 11 cases #178 and #615 each made an average of 1.4 flexions per retrieval on the smallest well (well 4), whereas case #1598 made an average of 9.0 flexions per retrieval (Fig. 1). The next day, a second motor-mapping procedure was conducted.

Phase II training. Phase II training included a titration procedure to encourage gradually more efficient retrieval of pellets from progressively smaller wells in the Klüver board. After 39 d of phase II training, criterion performance was reached. On the last day of phase II training, both the number of retrievals (772) and the finger flexions per retrieval (1.8) were similar to the performance levels of cases #178 and #615 after 11 d of phase I training. On the day after the phase II training, a third motor-mapping procedure was conducted.

Extinction. The animal was placed in its home cage for 4 months. During this time, no specific behavioral training was conducted. After this extinction period, a fourth motor-mapping procedure was conducted. After an *ad libitum* feeding period of 27 d, and then 2 d of food restriction, a behavioral probe was conducted on well 4 to gauge the effects of the extinction period on the animal's motor performance. The results of this behavioral probe showed that the animal's performance had reverted back to near-pretraining levels; that is, the number of retrievals fell to 122 pellets, and the flexions per retrieval rose to 4.75.

Reacquisition. Four and one-half months after the extinction map was generated, reacquisition training began. The procedure

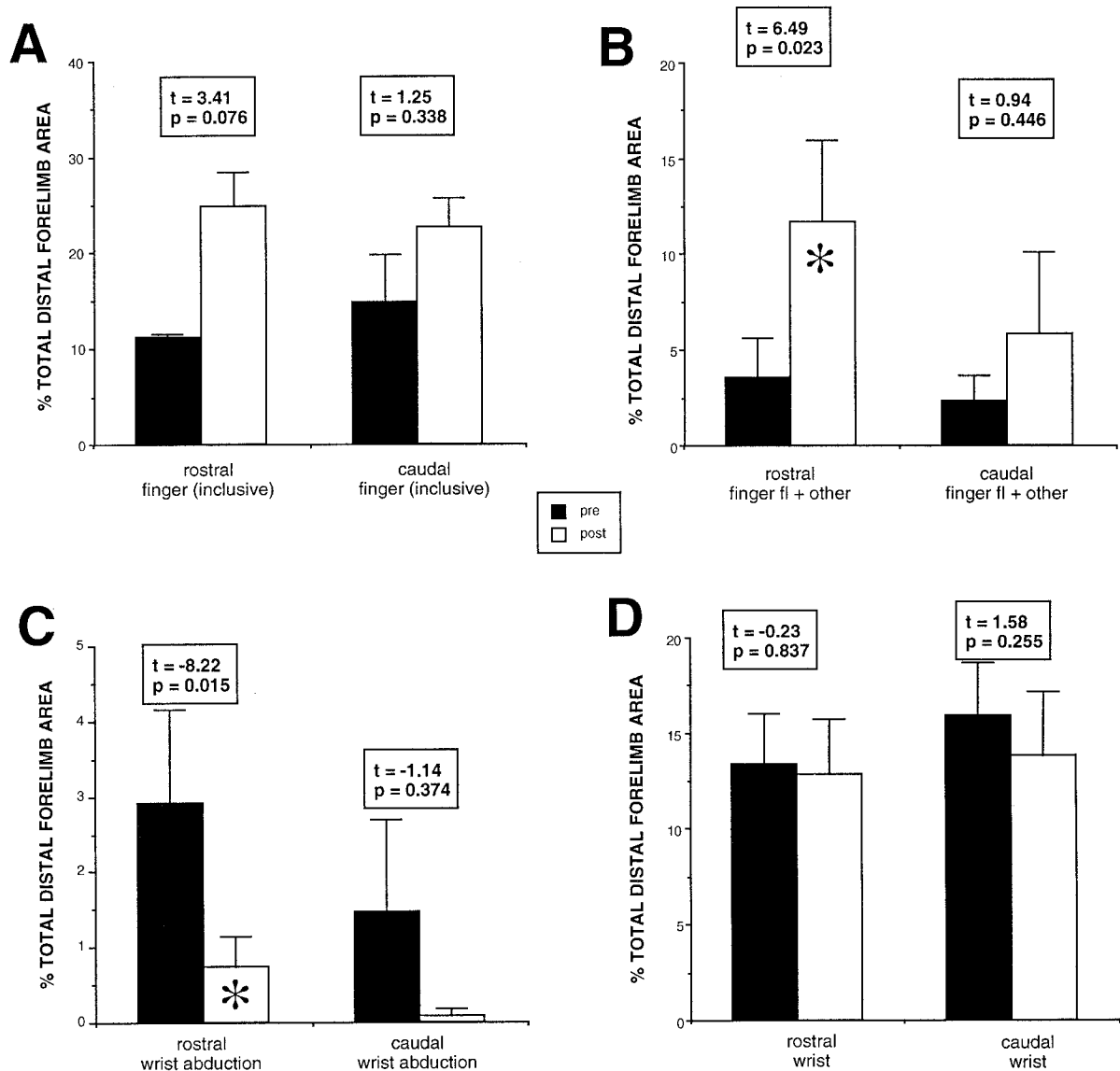


Figure 10. Changes in representation of selected movements in rostral and caudal sectors of distal forelimb representation after digit training. *A*, Percentage of finger (inclusive) area was increased in both rostral and caudal sectors after training, but this increase was somewhat larger (although not statistically significant) in the rostral sector. *B*, Percentage of finger flexion + other area (finger flexion dual-response area) was larger in both rostral and caudal sectors after training, but this increase was significant only in the rostral sector. *fl*, Flexion. *C*, Percentage of wrist abduction area was smaller in both rostral and caudal sectors after training, but was significant only in the rostral sector. *D*, Rostral–caudal differences were not evident in other movement representations, such as percentage of wrist area. Asterisks indicate statistically significant differences ($p < 0.05$). *pre*, Pre-training; *post*, post-training.

was identical to phase II training. The animal required 30 d to reach criterion performance during reacquisition compared with 39 d during initial training. On the last day of training, the animal's performance was better than at the end of initial training (number of retrievals = 1068; finger flexions per retrieval = 1.33). The next day, a fifth motor-mapping procedure was conducted. Behavioral performance during each of five training phases is summarized in Figure 11.

Movements and movement combinations used in behavioral task

To assess quantitatively the changes in movements and movement combinations used during each phase of the motor task, frame-by-frame analysis of videotapes was done. Samples consisting of selected trials at each of five stages of training on the smallest well (well 4) were examined. These were as follows: (1) baseline, the

first 5 trials; (2) phase I training, the first 25 trials on the last day of phase I training; (3) phase II training, the first 25 trials on the last day of phase II training; (4) extinction, 25 probe trials 29 d after the postextinction map; and (5) reacquisition training, the first 25 trials on the last day of reacquisition training. Note that to minimize the effects of training in the analysis of the baseline behavior, this sample consisted of the first 5 trials, rather than 25 trials in subsequent behavioral samples.

For each stage of training, the frequency of each movement category and movement combination was tallied and expressed as a percentage of total movement events for that stage (Table 3). Although this frame-by-frame analysis was useful in describing the frequency of most movement categories, the frequency of thumb movements was not obtained, because the thumb was usually pressed against the apparatus or hidden.

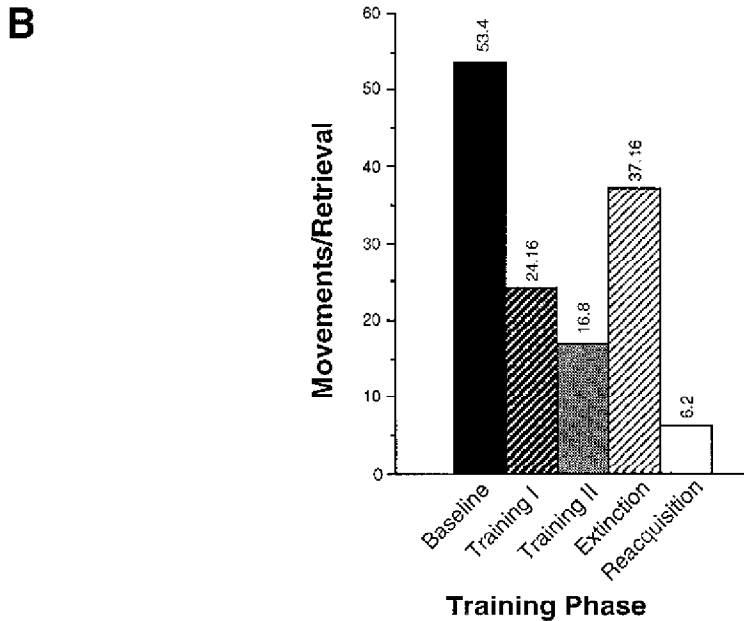
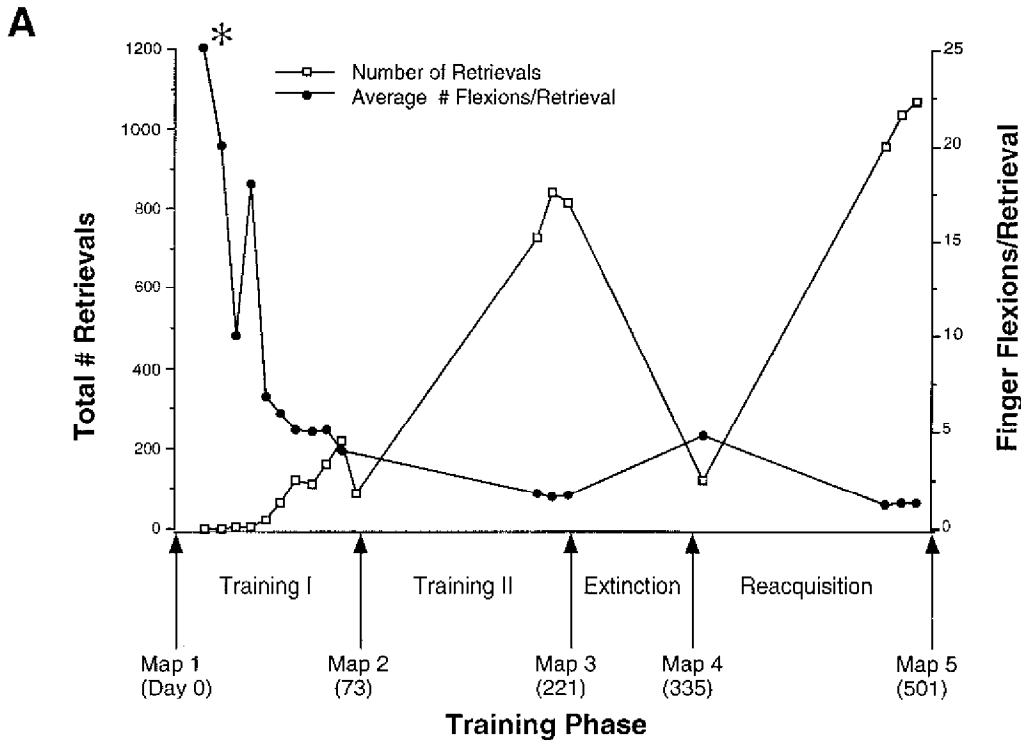


Figure 11. Progression of behavioral performance during five phases of a digit-training task. *A*, Double-Y plot showing number of retrievals (open squares) and average number of flexions per retrieval (filled circles). Day numbers refer to days after baseline mapping session (day 0). Time intervals on the x-axis are approximate. Asterisk indicates that no retrievals were obtained after 1200 flexions on the first day of training. *B*, Total number of movements/retrieval based on frame-by-frame analysis of videotapes after each of five phases of training.

The movement analysis showed three trends. First, as training progressed fewer total movements were made per trial (Fig. 11*B*). Along with the progressive decline in average number of flexions per retrieval (Fig. 11*A*), these results indicate that the animal's strategy became more efficient with training, involving fewer errors or unsuccessful movements. Second, movement combinations (e.g., finger flexion + wrist extension, etc.) became progressively more frequent. That is, the proportion of movements that comprised movement combinations increased with training (Fig. 12*D*, Table 3). Third, specific movements and movement combinations became more frequent during phases of training in which the behavioral performance was high, that is, at the end of phase II and reacquisition training (Fig. 12, Table 3). For example, the

combination of finger flexion and wrist extension constituted 1.0% of all distal forelimb movements in the baseline condition, decreased to 0.5% after phase I training (subcriterion performance), rose substantially to 29.3% after phase II training (criterion performance), dropped to 5.0% after extinction, and rose again to 21.3% after reacquisition (Fig. 12*F*, Table 3). It appeared that this combination was required for successful retrievals, because other movements or movement combinations resulted in a failure to retrieve pellets from well 4 even after phase II or reacquisition training. These results demonstrate that as training proceeded the animal's behavior became more efficient and stereotypic, resulting in a movement strategy that used a limited subset of specific movement combinations to complete the task successfully.

Table 3. Movements and movement combinations used in behavioral task (case #1598)

Individual movement categories			Movement combination categories		
Movement	Baseline (%)	Training II (%)	Movement	Baseline (%)	Training II (%)
Finger extension	39.20	56.69	Finger ext./F. pron.	9.05	25.13
Finger flexion	35.18	54.45	Finger ext./F. sup.	0.00	0.52
Wrist abduction	4.02	1.57	Finger fl./F. pron.	1.51	0.00
Wrist adduction	0.50	0.00	Finger fl./F. sup.	1.01	2.62
Forearm supination	23.12	34.55	Finger fl./Wrist ext.	1.01	29.32
Forearm pronation	23.12	35.60	Finger fl./Wrist fl.	0.00	0.00
Wrist flexion	0.00	1.05	Finger ext./Wrist ext.	1.01	0.52
Wrist extension	9.05	34.03	Finger ext./Wrist fl.	0.00	0.00
Total	134.17 ^a	223.56	Finger fl./Wrist abd.	0.50	0.52
			Finger fl./Wrist add.	0.50	0.00
			Finger ext./Wrist abd.	1.01	1.05
			Finger ext./Wrist add.	0.00	0.00
			Wrist ext./F. pron.	1.01	0.00
			Wrist fl./F. pron.	0.00	0.00
			Wrist ext./F. sup.	0.50	1.57
			Wrist fl./F. sup.	0.00	0.00
			Total	17.09	61.78

^aThe sum of the individual movements exceeds 100% because the categories are not mutually exclusive. That is, the movements listed in the table represent *inclusive* categories, similar to the hierarchical classification for ICMS-evoked movement categories. pron., Pronation; sup., supination. Other abbreviations as in Table 1.

Electrophysiological results

Analysis of distal forelimb representations in the five maps revealed that changes in the relative areal extent of several of these movement categories were appropriate for each of the five training phases preceding the mapping experiment. For example, the areal extent of the (inclusive) finger area declined slightly from the baseline map to the post-training I map from 40.3 to 34.5% of the total distal forelimb area. The inclusive finger area then rose to 55.9% in the post-training II map, declined to 45.2% in the postextinction map, then rose again to 51.2% in the post-reacquisition map. Also, the areal extent of several dual-response categories was highest after successful training and reacquisition (Figs. 12, 13).

In addition, the changes in relative area of several distal forelimb movement categories closely paralleled changes in the animal's behavioral performance. For example, double-Y plots in Figure 12 reveal that the relative areal extent of the finger flexion + wrist extension representation paralleled the number of retrievals obtained during each phase of behavioral training (Fig. 12B). In contrast, the relative wrist/forearm area was inversely related to the number of retrievals (Fig. 12C). Further still, the changes in relative area of other movement categories (each a dual-response category) paralleled changes in the frequency of these same movement combinations used to perform the task (Fig. 12D–F).

Changes in movement representations after forearm training

To determine whether changes in movement representations occur using a behavioral paradigm encouraging use of a different set of movements, we trained one animal to make repeated, stereotyped supinations and pronations by turning an eyebolt. The training procedure required a gradual shaping of the animal's forelimb movements over a period of 7 weeks as described in Materials and Methods. During supination, the animal also flexed the digits. Initially, the animal ceased manipulating the eyebolt upon delivery of each reward and retrieved the pellet manually from the trough. However, in the final stages of training, the animal invariably used one arm to turn the eyebolt, maintaining

constant contact, retrieving pellets from the automatic dispenser either with the opposite hand or with the mouth.

The results of two pretraining baseline maps and one post-training map are illustrated in Figure 14. Expressed as a percentage of total distal forelimb area, the areal extent of individual movement representations was relatively unchanged in the two baseline maps (see *error bars* in Fig. 14).

As in digit training, forearm training resulted in considerable changes in distal forelimb movement representations. However, the changes in specific movement categories were markedly different from those recorded after digit training and, in many respects, reflected the differences in movements used to accomplish the task. For example, the forearm-training case showed a *decrease* in the finger representation from 49% of the total distal forelimb area in both of the two pretraining maps to 30.9% in the post-training map. This decrease was attributable primarily to a decrease in the finger extension representation, which decreased from 26.5 and 35.9% in the two pretraining maps to 18.1% in the post-training map (Fig. 14).

In the digit-training cases described above, forearm supination remained relatively constant, increasing by 1.4 and 2.0% of the total distal forelimb area in two cases and decreasing by 3.4% in one case. In contrast, in the forearm-training case, forearm supination increased from 4.1 and 2.4% of the total distal forelimb area in pretraining maps, respectively, to 9.3% in the post-training map. Forearm pronation area remained unchanged, comprising 4.0 and 1.4% of the total distal forelimb area in pretraining maps and 2.6% in the post-training map. One other movement category, wrist abduction, displayed a substantial increase in representational area, increasing from 2.8 and 5.2%, respectively, in pretraining maps, to 11.2% in the post-training map.

To summarize, these two different training paradigms—one encouraging the increased use of the digits, the other encouraging the increased use of the forearm—resulted in very different changes in distal forelimb movement representations. Digit training led to an

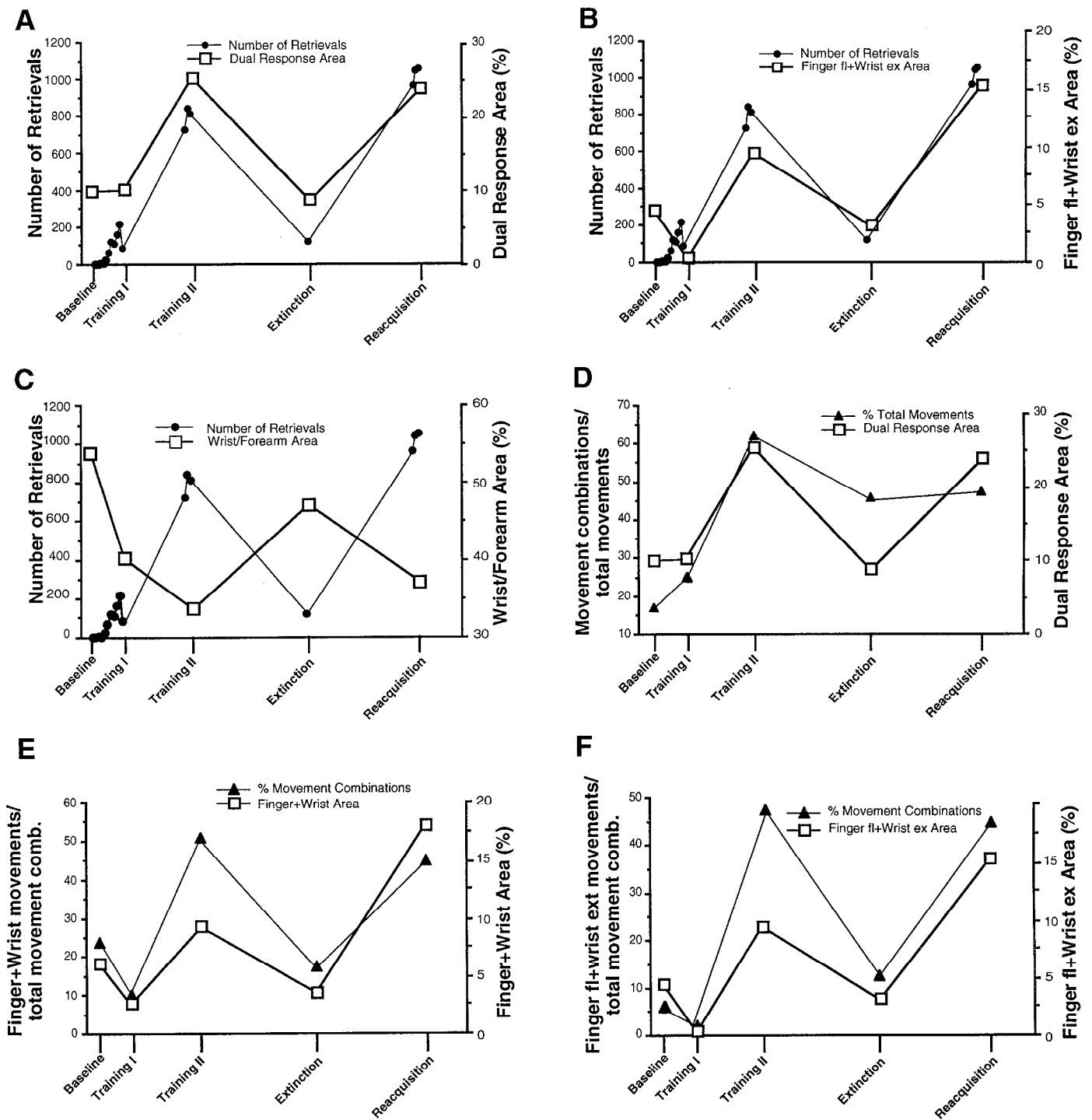


Figure 12. Double-Y plots showing parallel changes in behavioral performance and representational area after each of five phases of a digit-training task (case #1598). *A–C*, Behavioral performance is the total number of retrievals for selected training days before each mapping session; representational area is the total cortical area from which dual-responses, finger flexion + wrist extension, and wrist/forearm were evoked. *D*, Behavioral performance is the proportion of total movements comprising movement combinations. Note that this differs from Table 3, in which movement combinations are expressed as a proportion of total movements. Representational area is the percentage of distal forelimb area from which dual-responses were evoked. *E, F*, Behavioral performance is the proportion of movement combinations that were comprised of finger + wrist and finger flexion + wrist extension, respectively. Representational area is the percentage of distal forelimb area from which these same movements were evoked. See Results for further details. Time intervals on the *x*-axis are approximate. *comb.*, Combinations; *ex*, extension; *fl*, flexion.

increase in representational area devoted to fingers, including finger flexion and extension, and in dual-response areas involving finger movements, especially finger flexion and wrist extension. In addition, digit training resulted in a decrease in the representational area

devoted to wrist, especially wrist abduction. By contrast, forearm training resulted in an increase in representational area devoted to wrist abduction and forearm supination and a decrease in representational area devoted to finger extension.

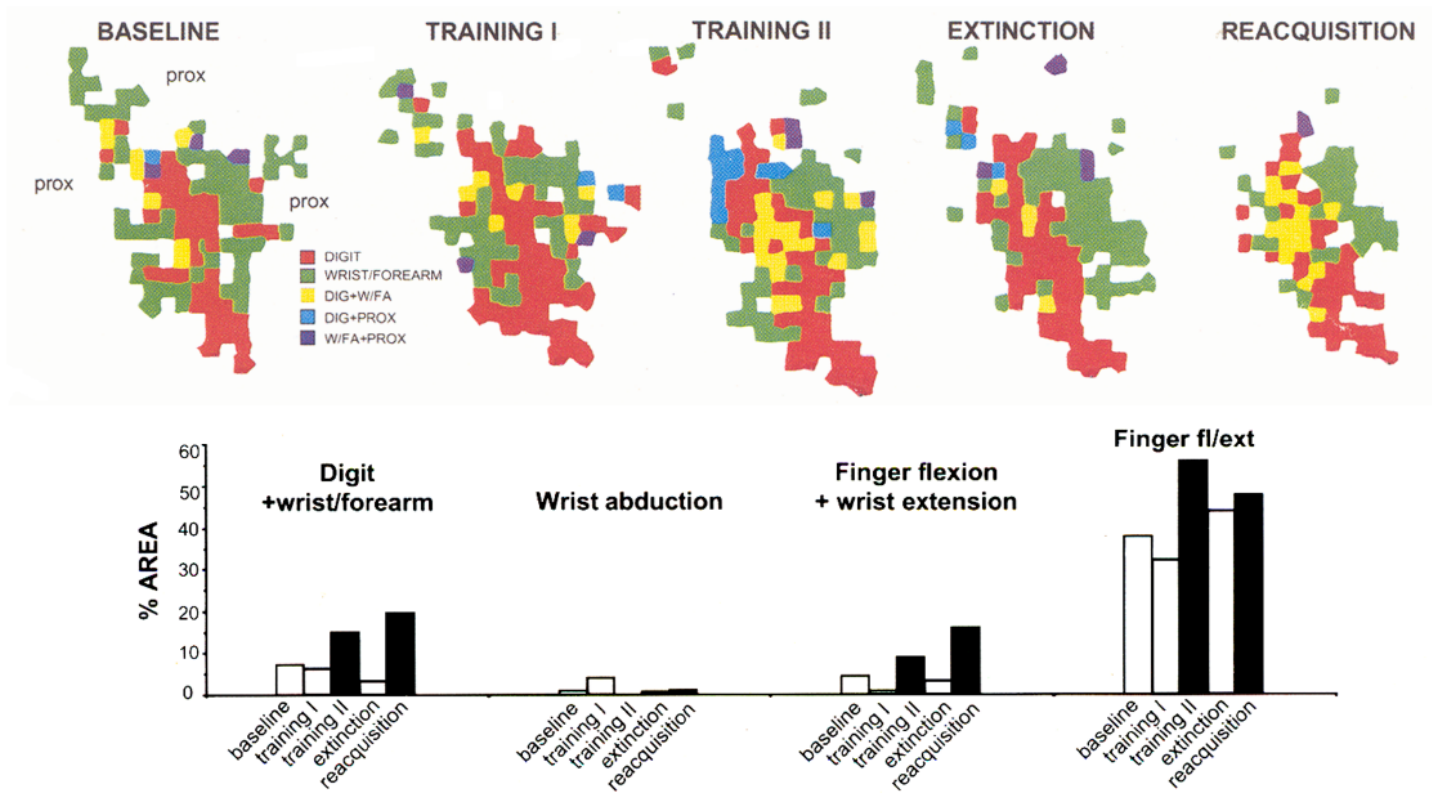


Figure 13. Changes in representation of selected movements after each of five phases of a digit-training task (case #1598). Phase I training was conducted on a Klüver board for 11 d and resulted in subcriterion performance. In phase II training (39 d), we used a titration procedure on the Klüver board, which resulted in criterion performance. During the extinction phase, no behavioral training was conducted for 4 months. The reacquisition phase (30 d) was identical to phase II training. The areal extent of several movement categories, especially categories consisting of combinations of digit and wrist movements, paralleled the behavioral training procedure. *DIG*, digit; *W/FA*, wrist forearm; *PROX*, proximal; *fl/ext.*, flexion/extension.

DISCUSSION

Before discussing the implications and functional significance of these findings, it is important to address possible sources of variability that may have contributed to the alterations in motor map organization recorded in these experiments.

Possible sources of variation in ICMS-defined motor maps

The significance of the areal changes in movement representations ultimately depends on the reliability of the ICMS technique used to determine the functional organization of M1. The sources of variability in movements evoked by ICMS have been discussed in detail in an earlier paper and by other investigators (Gellhorn and Hyde, 1953; Huang et al., 1988; Nudo et al., 1992; Sanes et al., 1992). However, two aspects of ICMS mapping procedures bear special importance for the present experiments. First, as has been observed in the past, ICMS sometimes evokes movements about multiple joints, even at threshold current levels. Because the interpretation of our results depends in part on the definition of movements evoked at these so-called dual-response sites, careful attention to the potential movement about each joint was required during the ICMS period. We used a standardized criterion for dual-responses: if a second movement was reliably evoked at $\leq 2 \mu\text{A}$ above the threshold intensity, the movements were said to be unresolvable and the site was designated as a dual-response site. The use of a second independent observer further ensured the reliability of these definitions.

Second, although we attempted to control the anesthetic state under ketamine/acepromazine as closely as possible, when neces-

sary we temporarily suspended ICMS mapping during periods of deeper or lighter than usual anesthesia. To the extent that variations in anesthetic state may be a significant source of variability in ICMS-defined thresholds, conclusions based on threshold data should be weakened accordingly. Nevertheless, it should be noted that the specific movements evoked by ICMS at a given site did not vary substantially throughout the course of the mapping procedure, despite a slight waxing and waning in anesthetic state.

Stability of ICMS-defined control maps

It is clear from the present data that ICMS-derived maps of movement representations are somewhat variable from one mapping procedure to the next, even in the absence of specific manipulations. Despite our attempts to control each of the potential sources of variability inherent in ICMS-mapping procedures, movement representations were not identical across time in the same cortical sector of area 4 of the same animal.

Nevertheless, the general topography of specific movement representations was approximately constant in control maps and was not substantially different from that of previously published distal forelimb maps in M1 [Donoghue et al. (1992) and Nudo et al. (1992) in squirrel monkey; Gould et al. (1986) and Stepniewska et al. (1993) in owl monkey; Huntley and Jones (1991) in macaque]. Changes that occurred were small and not consistent from case to case. It is tempting to speculate that even these changes in control cases were attributable to the experimental procedure itself, that is, the direct effects of the surgical intervention, the effects of the microstimulation procedure, and the indirect effects of the surgical intervention on the animal's behavior.

FOREARM TRAINING CASE 721: SELECTED MOVEMENT REPRESENTATIONS

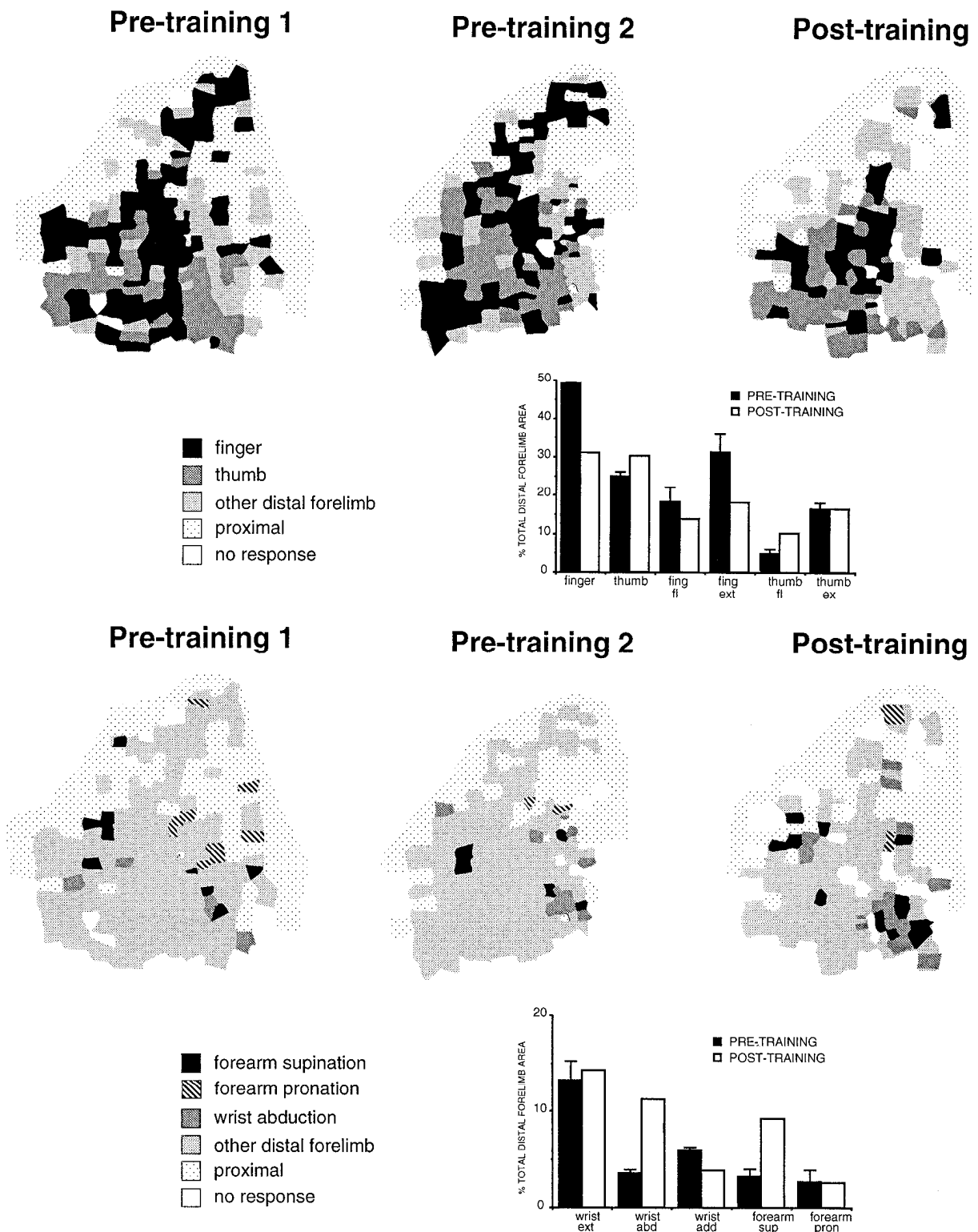


Figure 14. Representation of the distal forelimb in cortical area 4 before and after a training task requiring repetitive forearm supination and pronation. Each of the movement representations depicted in this figure is derived from inclusive categories, that is, they include dual-response sites. Abbreviations as in Tables 1 and 3.

Use-dependent reorganization of distal forelimb representations

In contrast to control cases, the movement representations of monkeys trained on a task requiring skilled movements of the digits changed systematically. The total distal forelimb area did not change significantly, increasing in the three trained animals by an average of 5%. Changes were found primarily in single-movement digit categories or in dual-response categories involving the combination of a digit movement and another distal forelimb movement (e.g., finger flexion/extension, finger flexion + wrist extension, etc.). These results suggest that as digit skills are acquired very little expansion of the total hand representation occurs. Instead, digit and wrist/forearm movement representations are redistributed within M1. In the present study, finger movement representations (and their combinations) expanded at the expense of wrist representations. In contrast, after training on a task requiring supination and pronation of the forearm, finger movement representations decreased in areal extent, whereas forearm supination and wrist abduction increased. Thus, specific behavioral tasks differentially alter movement representations.

In addition, a repeated mapping experiment derived from five phases of behavioral training suggest that use-dependent changes are progressive and reversible. However, reversibility was not complete after an extinction phase. Although behavioral performance dropped to pretraining levels, finger representations decreased by relatively small amounts (Fig. 12). This discrepancy between behavioral performance and representational area suggests that once a novel motor task is learned certain aspects of functional cortical topography remain altered for an extremely long period of time.

It is interesting to note that the animal in which behavioral performance was initially poor and required a long titration procedure to reach criterion performance on a digit-skill task (case #1598) also possessed unusually small distal forelimb representations, especially for finger extension. This finding, although anecdotal, suggests that the size of the cortical territory devoted to the hand is directly related to motor skill.

Many of the representational changes could be predicted by behavioral changes associated with the specific motor tasks. However, other changes were expected but not found. First, the lack of a substantial increase in the total distal forelimb area seems contradictory to earlier results. For example, other studies in adult rats demonstrated an expansion of the distal forelimb representation after peripheral nerve lesions (Sanes et al., 1988, 1990; Donoghue et al., 1990), electrical stimulation (Nudo et al., 1990), or passive movements (Humphrey et al., 1990). This apparent discrepancy may be attributable to at least two reasons: (1) in the present study manipulations were strictly behavioral, possibly inducing more subtle changes in cortical topography; (2) the behavioral task required use of muscles throughout the upper extremity, not just the distal forelimb. Thus, changes in elbow and shoulder representations may have counterbalanced, to some extent, expansion of more distal representations.

Second, because the combination of finger flexion and wrist extension seemed to be required for successful pellet retrieval, it was somewhat surprising that the finger flexion area did not change significantly. Significant changes with training occurred only when the finger flexion area was combined with the finger extension area. It is possible that independent finger extension (and finger stabilization) was required for the *insertion* of specific fingers into the well and that finger flexion + wrist extension was

required for *retrieval* (Fig. 2). Individual differences in the strategies that each animal used may have contributed to variations in finger flexion and finger extension expansion.

Third, after forearm training, the forearm supination representation increased in areal extent but the forearm pronation representation remained constant. No simple explanation can account for this discrepancy, because approximately equal force was required to activate the microswitches during each phase of movement. Future studies using electromyographic analysis of supinators and pronators should reveal whether these muscles are used symmetrically in this task.

Few significant changes in thresholds for activating movements were observed. This result suggests that the increase in areal extent of digit representations seen in this study was not the result of use-dependent changes in excitability of spinal cord motor neurons, as has been hypothesized previously (Leyton and Sherrington, 1917); that is, it is conceivable that a population of corticospinal neurons adjacent to a representational area, say the finger extension area, projects to motor neurons, innervating finger extension (i.e., extensor digitorum) muscles, but activation of these neurons results only in EPSPs in the motor neuron pool. After digit training, it is possible that a use-dependent increase in the excitability of the motor neurons allows activation of the same population of corticospinal neurons to *depolarize* motor neurons in the pool, resulting in finger movements from a more extensive area of cortex. Because no systematic decreases in threshold were found, this possibility is unlikely.

Only two significant changes in threshold, both increases, were observed. More current was required to evoke finger movements and finger extension movements after training. This result is important, because it implies that the higher currents required to evoke finger movements after training resulted in an “unmasking” of a preexisting representation. However, finger extension (as well as finger flexion) representations increased in areal extent after training even when movements were defined by using a fixed 20 μ A stimulus. Thus, it appears that individual movement representations expand independent of stimulation thresholds.

Development of task-specific combinations of movements (dual-response sites) as a correlate of motor learning

One of the most consistent results in the present study was that dual-response representations increased in total areal extent after digit training. Although dual-responses were evoked over a relatively small portion of the total distal forelimb area, they were evoked consistently over a *more* extensive area after training. It is interesting to note that the thresholds for evoking dual-responses are unusually low, especially after training (see Fig. 9)

In addition, examination of videotapes depicting movement strategies used in the acquisition of the digit task revealed that the movement combinations that were used more frequently after training were the same movements that were represented in these expanded dual-response areas. Perhaps more important, movement *combinations* used in the acquisition of a skilled motor task came to be represented in the *same* cortical territory. This result suggests that the temporal correlation of movements (and presumably, muscles) drives changes in cortical motor organization. Whether the mechanisms underlying these changes are attributable to temporally correlated outputs from motor cortex or temporally correlated inputs to motor cortex from activated muscles and joints cannot be delineated using the present techniques. However, these results suggest that a neurophysiological correlate

of a motor skill resides in M1 for at least several days after acquisition. The results also suggest that the combinations of movements evoked by ICMS are attributable partially to the specific temporally correlated movements used by the animal before the ICMS-mapping procedure.

The idea that temporally correlated input drives cortical organization has been suggested in several recent papers in auditory, somatosensory, and visual cortex (Merzenich et al., 1984; Merzenich, 1987; Miller et al., 1989; Singer, 1990; Allard et al., 1991; Recanzone et al., 1992a–c; Dinse et al., 1993). For example, it was shown recently in owl monkey that several weeks to months after suturing two digits so that they received temporally coincident input, double-digit receptive fields were found in primary somatosensory cortex (Allard et al., 1991). The present results are consistent with this hypothesis, because dual-response representations expanded in motor cortex after behavioral training that encouraged coincident movements represented in the expanded territories.

In contrast, some results were *not* consistent with this hypothesis. For example, after forearm training, changes in dual-response representations were not observed. Based on the strategy used to turn the key, one would expect an increase in the areal extent of the forearm supination + finger flexion representation. No such increase was found. In fact, the finger flexion area decreased slightly. It is possible that results from the present digit-training task cannot generalize to other tasks. Although unlikely, the emergence of dual-response zones may be correlated uniquely with tasks requiring skilled use of the digits. Also, individual differences in strategies used by different animals may result in very different patterns of reorganization in motor topography.

Rostral–caudal differences in use-dependent reorganization in M1

Although changes in movement representations were observed throughout the M1 distal forelimb area, they were larger and more consistent in the rostral half. This result may be important because it has been argued that M1 can be functionally subdivided into rostral and caudal zones based on sensory afferent distributions. Recent anatomical results in owl monkeys suggest that caudal M1 is connected primarily with area 1 of somatosensory cortex (and weakly with area 3b), whereas rostral M1 is connected primarily with area 2 and other motor areas [Stepniewska et al. (1993); see also Jones et al. (1978)]. Electrophysiological results also suggest that rostral and caudal M1 are functionally distinct. Tanji and Wise (1981) found in macaques that cutaneous units were confined primarily to caudal M1, whereas noncutaneous units predominated in rostral M1. In squirrel monkeys, we have found that although noncutaneous units responding to muscle and joint input are found throughout the M1 hand area, cutaneous units are confined to its most caudal aspect (Humphrey et al., 1994). Finally, Strick and Preston (1982b) also reported that caudal M1 receives primarily cutaneous afferents, whereas rostral M1 receives muscle and joint afferents. However, the relationship between the mosaical representations in M1 found in the present article (but see also Gould et al., 1986; Donoghue et al., 1992; Stepniewska et al., 1993) and the paired digit/wrist representations found by Strick and Preston is unclear. Combined with the present results demonstrating greater changes in representational plasticity in rostral M1, these data suggest that the activation of muscle and joint receptors by specific movements in a motor task plays an important role in the subsequent reorganization of M1.

As a corollary, the activation of cutaneous receptors by these same movements plays a less important role in reorganization in M1, at least in this particular task.

Mechanisms underlying use-dependent reorganization in motor cortex

Although the mechanisms underlying functional reorganization in motor cortex are difficult to interpret on the basis of techniques used in the present study, experiments in other laboratories have begun to shed light on a possible model. Recently, it has been shown that synaptic efficacy in motor cortex may be modified by the induction of long-term potentiation (LTP), similar to mechanisms that have been studied extensively in hippocampus (Iriki et al., 1989; Keller et al., 1990). Also, local modules within motor cortex are linked via both excitatory and inhibitory intracortical connections (Keller, 1993). In cortical slice preparations in rat motor cortex, LTP can be induced in local intracortical connections, providing a possible mechanism for synaptic plasticity in motor cortex (Keller et al., 1990; Hess and Donoghue, 1994). Application of *N*-methyl-D-aspartate antagonists to motor cortex in rat blocks plasticity induced by passive limb movement (Qiu et al., 1990). Finally, intracellular changes in synaptic effectiveness have been recorded as a consequence of classical conditioning in motor cortex in cat (Woody et al., 1991; Aou et al., 1992). It is possible that changes in synaptic efficacy between neighboring cortical modules underlie the increase in dual-responses seen in the present study. For example, in the baseline condition, ICMS in a particular locus in motor cortex may evoke finger flexion, whereas ICMS in another locus may evoke wrist extension. It is possible that combined use of finger flexion in combination with wrist extension during a motor task enhances intracortical connections between these two modules. Subsequently, ICMS can evoke both digit flexion and wrist extension at the same current level, because excitation of one module then engages the other.

Alternatively, changes in dual-responses evoked by ICMS in M1 may be the result of changes in synaptic efficacy in subcortical brain structures or in the spinal cord. For example, corticospinal neurons are known to branch extensively, often innervating multiple motor neuron pools (Fetz and Cheney, 1980; Shinoda et al., 1981). It is possible that efficacy of selected synapses is altered during motor training. However, according to this model a *decrease* in thresholds after training would be expected. As described above, decreases in threshold were not recorded.

Functional significance of use-dependent reorganization in motor cortex

Large changes in topographic organization after acquisition of behavioral tasks have been observed previously in somatosensory, auditory, and visual cortices (Jenkins et al., 1990; Recanzone et al., 1992b,c, 1993). The present experiments extend these findings to M1 (see also Suner et al., 1993). Thus, they represent an important test of the general hypothesis that representational maps are a reflection of individual experiences.

Earlier experiments by Woody and Engel (1972) have demonstrated that large changes in movement representations arise in the motor cortex of Pavlovian-conditioned cats. Specific changes in those studies were related to conditioned responses or to unconditioned stimuli (for review, see Woody, 1986). Fetz and Baker (1972) have shown that isolated cells in motor cortex can be operantly conditioned to increase or decrease their firing rate within minutes. Although these experiments were not designed to provide a reconstruction of changes in the detailed topographies

of motor representations, they argue strongly that at least the classical conditioning paradigm produces significant changes in distributed neuronal responses in motor cortex.

Recent studies in humans using a variety of techniques have also suggested that primary cortical areas are alterable as a result of motor skill learning. For example, in positron emission tomographic studies, activation of the hand area in M1 was found to increase as subjects practiced sequences of finger movements (Seitz et al., 1990; Grafton et al., 1992; Jenkins et al., 1994; Remy et al., 1994; Schlaug et al., 1994). Using transcranial magnetic stimulation to map the motor cortex, Pascual-Leone et al. (1994) found that improvement in reaction time on a motor task was correlated with enlargement in the output maps of muscles engaged in the task. More recently, using functional magnetic resonance imaging, the extent of motor cortex activated during performance of a motor sequence was found to increase (Karni et al., 1994).

Acquisition and execution of a skilled motor task require the coordinated participation of a number of structures in the motor hierarchy, including motor cortex, basal ganglia, cerebellum, and spinal cord. It is unreasonable to assume that motor cortex is the only locus for use-dependent reorganization in motor systems (Aizawa et al., 1991; Aosaki et al., 1994). It is almost certainly the case that neuronal programs for motor skills are distributed, as has been suggested for storage of memory (Squire, 1992). However, the present results suggest that at least some aspects of acquired motor skills are reflected in the topography of neurophysiological maps in M1.

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