

Effects of Repetitive Motor Training on Movement Representations in Adult Squirrel Monkeys: Role of Use versus Learning

Erik J. Plautz,* Garrett W. Milliken,† and Randolph J. Nudo‡,§

**Department of Neurobiology and Anatomy, University of Texas–Houston, Houston, Texas 77030;*

†*Department of Psychology, College of Charleston, Charleston, South Carolina 29424; and*

‡*Department of Molecular and Integrative Physiology and §Center on Aging, University of Kansas Medical Center, Kansas City, Kansas 66160*

Current evidence indicates that repetitive motor behavior during motor learning paradigms can produce changes in representational organization in motor cortex. In a previous study, we trained adult squirrel monkeys on a repetitive motor task that required the retrieval of food pellets from a small-diameter well. It was found that training produced consistent task-related changes in movement representations in primary motor cortex (M1) in conjunction with the acquisition of a new motor skill. In the present study, we trained adult squirrel monkeys on a similar motor task that required pellet retrievals from a much larger diameter well. This large-well retrieval task was designed to produce repetitive use of a limited set of distal forelimb movements in the absence of motor skill acquisition. Motor activity levels, estimated by the total number of finger flexions performed during training, were matched between the two training groups. This experiment was intended to evaluate whether simple, repetitive motor activity alone is sufficient to produce representational plasticity in cortical motor maps. Detailed analysis of the motor behavior of the monkeys indicates that their retrieval behavior was highly successful and stereotypical throughout the training period, suggesting that no new motor skills were learned during the performance of the large-well retrieval task. Comparisons between pretraining and posttraining maps of M1 movement representations revealed no task-related changes in the cortical area devoted to individual distal forelimb movement representations. We conclude that repetitive motor activity alone does not produce functional reorganization of cortical maps. Instead, we propose that motor skill acquisition, or motor learning, is a prerequisite factor in driving representational plasticity in M1. © 2000 Academic Press

We thank Grey Gardner, Cami Knox, and Ramin Raiszadeh for assistance with data collection, Patricia Pohl and Dennis Wallace for helpful discussions, and Scott Barbay, Kathleen Friel, Jeff Kleim, Diane Larson, and Haiying Wang for comments on an earlier version of the paper. This work was supported by MH 10963 (E.J.P.), NS 09366 (G.W.M.), NS 27974 and NS 30853 (R.J.N.), Center Grant HD02528 from NICHD, and the American Heart Association.

Address correspondence and requests for reprints to Randolph J. Nudo, Center on Aging, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160. Fax: (913) 588-1201. E-mail: rnudo@kumc.edu.



Key Words: motor cortex; intracortical microstimulation (ICMS); squirrel monkey; motor learning; motor activity; representational mapping; cortical plasticity; hand; nonhuman primates.

Recent investigations in several sensory and motor cortical areas have demonstrated that the functional organization of representational maps is dynamic and reflects the experiences of the organism (Buonomano & Merzenich, 1998; Byl, Merzenich, & Jenkins, 1996; Donoghue, 1995; Dykes, 1997; Kaas, 1991; Kilgard & Merzenich, 1998; Merzenich, Recanzone, Jenkins, Allard, & Nudo, 1988; Milliken, Plautz, Gardner, Raiszadeh, & Nudo, 1994; Milliken, Plautz, & Nudo, 1995; Nudo, Jenkins, Merzenich, Prejean, & Grenda, 1992; Nudo, Milliken, Jenkins, & Merzenich, 1996; Weinberger, 1995; Weinberger & Bakin, 1998). In particular, it has become apparent that repetitive motor behavior can produce changes in representational maps in motor cortex (Kleim, Barbay, & Nudo, 1998; Nudo et al., 1996; Nudo, Plautz, & Milliken, 1997). Still, it remains unclear which specific aspects of the ongoing motor behavior are responsible for producing this functional plasticity.

Numerous noninvasive functional imaging studies in human subjects have indicated that primary motor cortex (M1) is involved in the process of motor learning (e.g., Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Pascual-Leone, Grafman, & Hallett, 1994; Schlaug, Knorr, & Seitz, 1994; Seitz, Roland, Bohm, Greitz, & Stone-Elander, 1990; Zhuang, Dang, Warzeri, Gerloff, Cohen, & Hallett, 1998). Further, it has been noted that learning-associated activity in M1 can be greater in magnitude and areal extent than the activity associated with simple motor use (Grafton, Mazziotta, Presty, Friston, Frackowiak, & Phelps, 1992; Karni, Meyer, Jezzard, Adams, Turner, & Ungerleider, 1995; Kawashima, Roland, & O'Sullivan, 1994; Pascual-Leone, Dang, Cohen, Brasil-Neto, Cammarota, & Hallett, 1995). These studies suggest that, at least in humans, the learning process may affect the functional organization of M1 differently than the process of movement execution.

In animal studies, several lines of evidence support a role for motor learning in the production of functional changes in motor cortex. Single-unit recording studies in awake, behaving animals have indicated that the neural activity of individual motor cortical units can be modulated as a function of skill learning (Aizawa, Inase, Mushiake, Shima, & Tanji, 1991; Germain & Lamarre, 1993; Mitz, Godschalk, & Wise, 1991). In cortical slice preparations, it was recently shown that the capability of motor cortical neurons to undergo synaptic long-term potentiation and long-term depression can be altered by prior motor skill training (Friedman, Rioult-Pedotti, & Donoghue, 1997). Representational mapping studies in squirrel monkeys have demonstrated that motor training paradigms can produce systematic changes in M1 representational maps, such that improvements in a motor skill are correlated with expansions of specific movement representations in M1 (Nudo et al., 1996). Taken together, these findings in human and animal models indicate that behaviorally driven functional plasticity is a characteristic feature of motor cortex.

Although it is increasingly clear that motor behavior associated with skill learning plays a role in shaping the functional organization of M1, little is known about the relative contribution of simple motor use, independent of the learning process, to the production of plasticity in M1. To address this issue, we have examined the effects of motor training

on the representation of movements in M1. In this report, we present the results of training on a task that was designed to promote consistent, repetitive use of a limited set of forelimb movements without the necessity of learning a new motor skill in order to perform the task. These results are compared to a previous study in the same laboratory using identical neurophysiological techniques (Nudo et al., 1996) that demonstrated systematic changes in movement representations after training on a task that did require the learning of a new manual skill. Thus, we intended to evaluate whether repetitive motor use alone, in the absence of motor skill acquisition, is sufficient to produce a reorganization of cortical movement representations in M1. Preliminary results of this study have been previously reported in abstract form (Plautz, Milliken, & Nudo, 1995).

MATERIALS AND METHODS

Seven adult male squirrel monkeys (genus *Saimiri*) were used in the present study. Four animals served as controls, and three others participated in a motor training task. Monkeys were individually housed throughout the course of the experiment. The general procedure for each animal was as follows. After the monkey's hand preference was determined, a baseline motor mapping procedure (map1) was performed in primary motor cortex (M1). Then, after a 2- to 3-week recovery period, animals in the training group were trained on the motor task. For both groups, a second mapping procedure (map2) was performed approximately 4–5 weeks after map1. Control animals received no training between map1 and map2. In one monkey (9409), the map–train–remap procedure described above was repeated 6 months after the initial experimental procedure was completed. This “retraining” procedure is treated as a separate experimental case in this report (designated “9409a” and “9409b,” respectively). Thus, a total of four map–remap procedures (control group) and four map–train–remap procedures (training group) were completed. Details of the behavioral, surgical, and neurophysiological methods are described below.

Hand Preference Determination

Several weeks prior to the initial neurophysiological mapping procedure, hand preference for the behavioral task was assessed using a modified Klüver board. This device consisted of a Plexiglas board containing five food wells of different diameters (25, 19.5, 13.5, 11.5, and 9.5 mm) that was secured to the front of the animal's home cage. The testing procedure consisted of retrieving banana-flavored food pellets (45 mg, Bioserv) from each of the five wells, presented pseudo-randomly such that the number of trials on each well was approximately equal. Fifty trials were performed on 2 separate days, for a total of 100 trials. The purpose of this brief exposure was to minimize any possible training-related effects while permitting an accurate assessment of the animal's preferred retrieval hand for this task. Testing sessions were videotaped for later analysis. The hand used on the majority of trials was defined as the preferred hand. See Nudo et al. (1992) for additional details. Two of the control monkeys were right-handed and two of the control monkeys were left-handed on the retrieval task. All three monkeys in the training group were right-handed on this task. Subsequent mapping procedures were conducted in M1 contralateral to the preferred hand.

Surgical Details and Methods

All surgical procedures were conducted under aseptic conditions and in accordance with approved animal protocols. Following an initial anesthetic dose of ketamine (20 mg/kg im), the trachea was intubated and the saphenous vein was catheterized for intravenous delivery of fluids and drugs. The monkey was then placed in a stereotaxic frame, halothane/nitrous oxide anesthesia was initiated, and warm (37°C) mannitol was given intravenously to reduce the likelihood of brain edema. A craniotomy ($\sim 1.5 \times 1.5$ cm) was performed contralateral to the preferred hand, roughly centered over the lateral extent of the central sulcus, and the overlying dura was excised. The bone flap was placed in sterile saline and stored at 4°C. A plastic chamber was attached to the skull with dental acrylic and filled with sterile silicone oil (dimethylpolysiloxane, Dow 200 fluid) to prevent desiccation of the cortex. Gas anesthesia was then withdrawn, and ketamine (~ 20 mg/kg/h), supplemented by either diazepam or acepromazine (~ 0.01 mg/kg/h), was given intravenously, as needed, throughout the remainder of the experiment. Intravenous fluids (lactated Ringers with 5% dextrose, ~ 10 cc/kg/h) were continuously delivered, penicillin (0.15 ml, 45,000 U) was given subcutaneously prior to surgery and at the conclusion of the experiment to reduce the possibility of infection, and physiological vital signs (heart rate, respiration rate, blood saturated O₂ level, and expired CO₂ level) were monitored and maintained within physiological ranges throughout the surgical and neurophysiological procedures. At the conclusion of the experiment, administration of intravenous anesthesia was halted, gas anesthesia was reinstated, the plastic chamber was removed, the dura was replaced by gelfilm, and the bone flap was secured with dental acrylic. The skin incision was closed with silk sutures and treated with a local anesthetic (Marcaine; approx. 1 cc) and a topical antibacterial agent (Furazolidone). Gas anesthesia was halted, and the monkey was removed from the stereotaxic frame and monitored in a temperature-controlled incubator until recovery from anesthesia was complete. The entire surgical and neurophysiological procedure typically required 15–20 h to perform.

Neurophysiological Procedures

After completion of the craniotomy, a magnified image of the cortical surface was digitally captured on an Apple Macintosh computer using a high-resolution video camera (Cohu) and NIH Image software (available at <http://rsb.info.nih.gov/nih-image/>) and transferred to a graphics program (Canvas, Deneba Software) for use during intracortical microstimulation (ICMS) mapping (Fig. 1A). The image of the cortical surface was used to visually site and record the location of electrode penetrations for ICMS with respect to the surface vasculature. These vascular landmarks permitted repeated mapping of nearly identical locations in subsequent mapping procedures. Sharply beveled glass micropipettes (15–25 μ m external diameter tip) filled with 3.5 M NaCl solution (500 to 800-k Ω impedance) were introduced perpendicular to the cortical surface on a grid pattern (~ 250 - μ m interpenetration distance) and lowered to a cortical depth of 1700–1800 μ m for detailed mapping of layer V motor outputs (Figs. 1A and 1B). The ICMS stimulus consisted of thirteen 200- μ s pulses delivered at 300 Hz (3.3-ms interpulse interval), resulting in a pulse train of 39.6-ms duration. The entire pulse train was repeated at 1 Hz until the evoked movements were defined, which typically required less than 1 min. Definition of movements was performed visually by one observer and confirmed by at least one additional

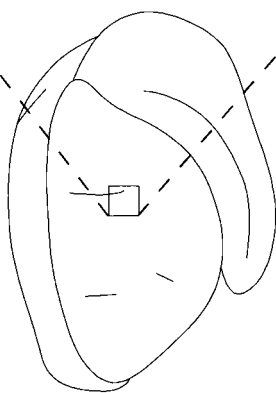
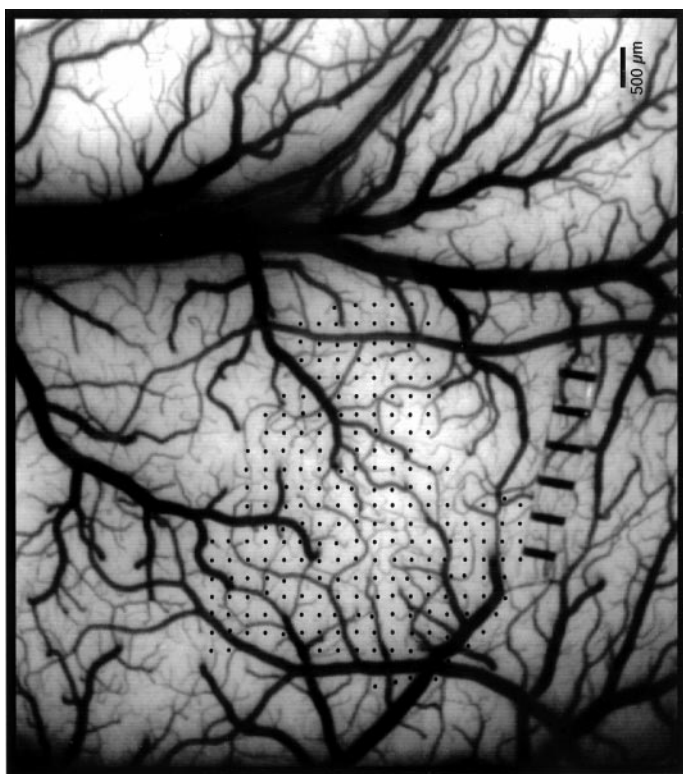
observer. A second observer independently reconfirmed the response at approximately 5% of the stimulated sites. The threshold for evoking movements was determined by slowly increasing the current from 0 μA until a movement was detected, up to a maximum of 30 μA . When a second movement around a different joint was evoked at 2 μA or less above threshold, the site was operationally defined as a “dual-response” site. If no movements were detected up to 30 μA , the site was classified as nonresponsive. Mapping continued until the entire extent of the distal forelimb representation was circumscribed either by sites from which proximal joint movements (e.g., elbow or shoulder) were evoked or by nonresponsive sites. Typically, maps were composed of 225–350 total sites (Fig. 1C). Nonresponsive sites that were determined to be within or immediately adjacent to the hand area were retested at the conclusion of the mapping experiment in order to rule out the possibility of anesthesia-related nonresponsiveness.

Analysis of Neurophysiological Mapping Data

Based on the relative locations of the electrode penetrations made during the experiment, two-dimensional topographic maps of movement representations were generated by an in-house computer program that uses an algorithm to establish unbiased borders midway between different representational regions (see Nudo et al., 1992, 1996 for details). The maps were then analyzed for the total areal extent of various movement types or categories using an image analysis program (NIH Image). Evoked movements were classified into a previously described set of hierarchically related categories (Nudo et al., 1992), such that general movement categories (e.g., total distal forelimb, digit, wrist/forearm) could be subdivided into more specific categories (e.g., finger, thumb, finger flexion, finger extension) as well as various combinations of these categories. Areal data for each category were converted to a percentage of the total distal forelimb (Nudo et al., 1996), normalized using the arcsin transformation (Zar, 1984), and then compared using a repeated-measures ANOVA to identify differences between map1 and map2 for both the control and the training groups. Percentages of total distal forelimb area were used in the analysis to reduce the variance due to individual subject-by-subject differences in absolute representational areas (see Nudo et al., 1992, 1996). A group (training vs control) by condition (map1 vs map2) interaction was taken to indicate an experience-dependent change in a given representational category. Categories comprising less than 2% of the total distal forelimb area (averaged across all maps) were eliminated from statistical analysis, in order to exclude categories for which evoked responses were rarely observed and which may not be biologically significant (see Nudo et al., 1996).

Behavioral Training and Data Analysis

Training was conducted on the largest well of the Klüver board (25-mm diameter; see Figs. 2 and 3A). The large well was wide enough for the monkeys to insert their entire hand during pellet retrieval. This task is readily performed by naive squirrel monkeys, thus eliminating the need for specific shaping procedures. Monkeys were first allowed to recover in their home cage for 2–3 weeks following the initial mapping procedure. Then, food was reduced for 24–36 h prior to the first training session to increase motivation. Training was conducted daily during two 30-min sessions (approx. 6–8 h apart) and each

**A**

session was videotaped for later analysis. Each trial began with the placement of a food pellet into the large well and ended when the animal retracted its hand back into the cage following a successful pellet extraction. Animals were allowed to retrieve and consume an unlimited number of pellets during each session. The number of pellets consumed daily was tallied and supplemental food given at the end of each training day, if needed, to maintain an adequate level of food intake (approx. 3% of ad libitum body weight per day). Due to the large number of pellets consumed as training proceeded, supplemental food generally was not needed after 2 or 3 days of training. Training continued until the task performance criterion was met, as follows. In a previous study of the effects of small-well training on motor representations (Nudo et al., 1996), individual monkeys performed approximately 12,000 discrete finger flexions over the course of training (11 days). To facilitate comparisons between the effects of large-well and the effects of small-well training on motor representations, a task criterion of 12,000 total finger flexions was used to indicate the end of the training period for the monkeys in the large-well training group. Only flexions made with the animal's preferred hand were used to determine when the task criterion had been reached. This resulted in a training period of 15, 13, 13, and 16 days for subjects 9409a, 9409b, 9418, and 9502, respectively. The posttraining mapping procedure was conducted within 24 h of the conclusion of the training period. As previously indicated, control animals did not undergo any training procedures on the Klüver board.

Videotaped sessions were examined for the number of flexions made with each hand during each trial, the hand used to successfully retrieve the pellet in each trial, and the total number of successful retrievals made with each hand during the session. These data were used to assess the animal's daily retrieval efficiency (total flexions per total retrievals) with the preferred hand. In addition, a daily error-rate was calculated, defined as the ratio of the total number of trials with more than one finger flexion over the total number of trials performed. The stability of values for number of pellets retrieved, efficiency, and error-rate performance measures was evaluated by first dividing the data into three segments (days 1–4, days 5–8, and days 9–end), normalizing percentage values (error-rate) using the arcsin transformation, and then calculating a one-way ANOVA to compare mean pellet number, mean efficiency, and mean error-rate for each segment.

In addition, a detailed frame-by-frame videotape analysis was used to determine the specific movement patterns each individual animal used during the performance of the task as well as the speed at which these movements were performed. Four training "epochs," represented by four evenly spaced days throughout the subjects' training period, were examined for each subject. The first 20 trials from both the morning and the afternoon sessions were examined, for a total of 40 trials per day (640 total trials examined).

For the movement pattern analysis, only those movements of the distal forelimb that were used to successfully extract the pellet from the well were recorded. These movements were defined as occurring while some portion of the hand (typically the fingers) was still within the volume of the food well. Thus, any distal forelimb movements performed during the reach toward and retraction from the well were not recorded. Any movements of the proximal joints (i.e., elbow and shoulder) during pellet extraction were not recorded either, since these movements were not clearly visible in every trial on the videotaped records. Specific movements tallied included movements of the fingers (flexion, extension), wrist (flexion, extension, radial deviation, ulnar deviation), and forearm (pronation, supination). It is possible that animals could use multiple movements during a single trial to

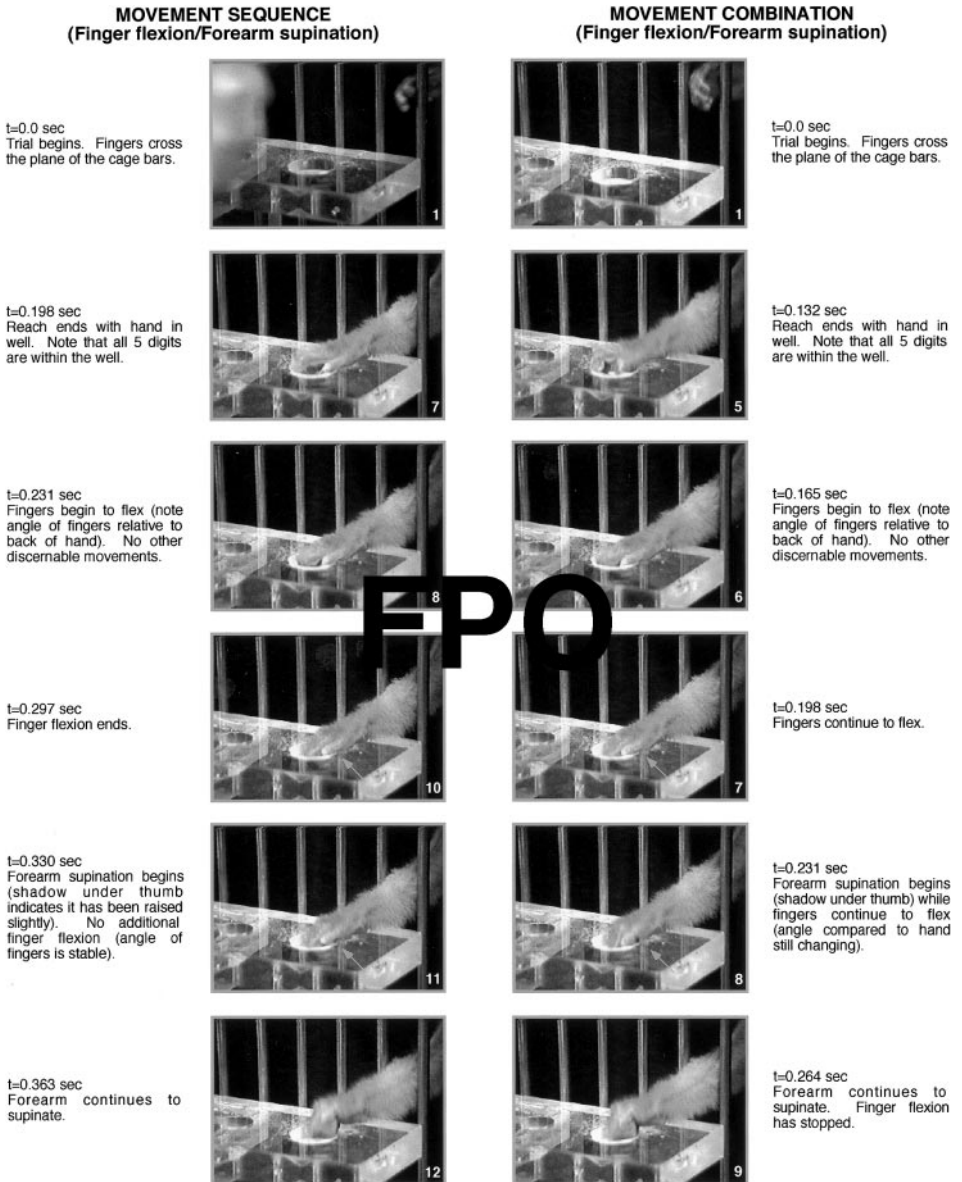


FIG. 2. Digitized video images illustrating the difference between a movement sequence (**left**) and a movement combination (**right**). Actual frame number is printed in lower right corner. Images obtained from subject 9502 on day 13. In this illustration, the forearm supination begins one frame after the finger flexion ends (**left**, frames 10–11) or it begins during the frame containing the final finger flexion movement (**right**, frames 7–8). *Green arrows* indicate position of thumb on the surface of the board (no shadow) prior to the start of the supination. *Blue arrows* indicate the slight separation of the thumb from the surface of the board (shadow), indicating that the supination has begun. The single-frame timing difference between movement sequences and movement combinations illustrated here was the most common difference observed in this study, with longer timing separations being extremely rare (data not shown).

perform a successful pellet extraction. When this was observed, care was taken to document the relative timing of the multiple movements. Multiple movements could occur consecutively (i.e., without any degree of temporal synchrony) or could occur at the same time (i.e., with either partial or complete temporal synchrony). Movements that occurred consecutively were defined as movement *sequences*, while movements that occurred simultaneously were defined as movement *combinations*. Figure 2 illustrates the difference between a movement sequence and a movement combination. Although identical movements could be performed as a sequence on one trial, and as a combination on another trial, as in Fig. 2, these movements were classified as two unique movement *patterns*. Each identified movement pattern is referred to in this report by a unique designation, P#, where # is an integer (see Table 2 for pattern descriptions). These data were used to evaluate the degree of stereotypy (i.e., consistency of movement patterns) exhibited during pellet retrievals from the large well. The stability of pattern use during training was evaluated by first calculating the percentage use of each observed movement pattern within each session, transforming the data (arcsin transform), and then comparing each epoch using a one-way ANOVA.

Finally, the speed of movement was evaluated during each training epoch. Three latency values were recorded: the time needed to reach from the cage to the training well and remove the pellet from the well (latency to extract, LE), the time needed to return the hand to the cage after successful extraction of the pellet (latency to retract, LR), and the total time from the initial reach toward the well until the hand was returned to the cage (total latency to retrieve, LT). Latency to retrieve was equal to the sum of latency to extract and latency to retract. Latency values were calculated by counting the number of video frames involved in each event and converting this number to milliseconds. Since the frame rate was 30 frames per second, each frame was equivalent to 33 ms. Trials with multiple flexions were excluded from the latency analysis (16 of 640 trials). Statistical comparisons were made using a one-way ANOVA (comparing time by epoch for each latency measure).

Although subject 9409a was trained for 15 days, no videotape was available to examine after day 10. Thus, it was not possible to evaluate extraction movements or latency values near the end of this subject's training period. Since the available data for efficiency and error-rate suggested that this subject's behavior remained stable during days 11–15, day 10 was treated as the final day of training for the purpose of defining the four training epochs.

RESULTS

The goal of this study was to evaluate the influence of adaptations in motor behavior on motor representations in primary motor cortex (M1). Specifically, we were interested in whether or not repetitive motor use, in the absence of motor skill learning, can effect changes in the organization of M1 motor maps. Therefore, it was first necessary to determine which motor behaviors, if any, were altered during the performance of a motor task designed to promote repetitive motor use. Then, motor map organization was compared before and after training on the motor task.

Behavioral Results

Several different measures of motor behavior were examined in detail in order to thoroughly evaluate (a) the range of motor behaviors used during the task and (b) whether

any degree of skill acquisition occurred during task performance. This analysis provides a basis for interpreting the results of the motor mapping procedures.

Number of pellets retrieved. For each of the four subjects, the number of pellets retrieved per day increased over the course of the training period from an average of 624 pellets on day 1 to an average on 965 pellets on the final day of training (Table 1). The greatest daily increases tended to occur early in training, followed gradually by achievement of asymptotic pellet retrieval levels (Figs. 3C–3F). Statistical comparisons made between three segments of the training period (days 1–4, days 5–8, and days 9–end) revealed that, for the entire group, there was a significant increase in the number of pellets retrieved over time ($p = .0002$, one-way ANOVA). This increase occurred between the first and the second segments of the training period ($p = .0005$, Fisher's PLSD post hoc) and was statistically stable thereafter.

Retrieval efficiency and error-rate. For each day of training, retrieval efficiency was assessed by calculating the ratio of total number of finger flexions to total number of retrievals (flex/ret). In each of the four subjects, retrieval efficiency was near-optimal initially (less than 1.1 flex/ret; optimal performance defined as 1.0 flex/ret) and remained at near-optimal levels throughout the training period (Figs. 3C–3F; Table 1). For the entire group, there were no significant variations in retrieval efficiency over time for three segments of training ($p = .893$; one-way ANOVA). Motor performance was also assessed by calculating an error-rate for each day of training for each subject. Error-rate is defined as the percentage of trials on which more than one flexion was needed to retrieve a pellet. For each of the four large-well training subjects, the error-rate was found to be very low; the mean for all four subjects was only 3% of trials (Fig. 3B; Table 1). For the group, there were no significant variations in error-rate over time for three segments of training ($p = .855$; one-way ANOVA). A strong linear correlation was found between efficiency and error-rate ($r = .967$, $p < .0001$). Taken together, these results indicate that the motor performance of monkeys trained on the large-well task was stable, efficient, and highly successful throughout the entire training period.

Movement patterns used during pellet retrieval. The results above suggest that the motor skills needed to perform the large-well retrieval task already existed within the motor repertoire of these monkeys prior to training. However, it is possible that retrievals could have been performed using any number of different, but equally efficient, motor

TABLE 1
Task Performance Data

Subject	Total No. of flexions	Number of pellets retrieved			Retrieval efficiency (flexions per retrieval)			Error-rate (%) (average \pm SD)
		Day 1	Final day	Average	Day 1	Final day	Average	
9409a	13,586	569	802	906	1.08	1.00	1.02	1.2 \pm 2.0
9409b	12,792	842	1123	942	1.01	1.04	1.04	4.2 \pm 2.6
9418	12,363	614	1033	940	1.04	1.01	1.01	1.1 \pm 0.8
9502	12,939	471	901	766	1.06	1.06	1.06	5.4 \pm 1.5
Group (average)	12,920	624	965	889	1.05	1.03	1.03	3.0 \pm 0.7

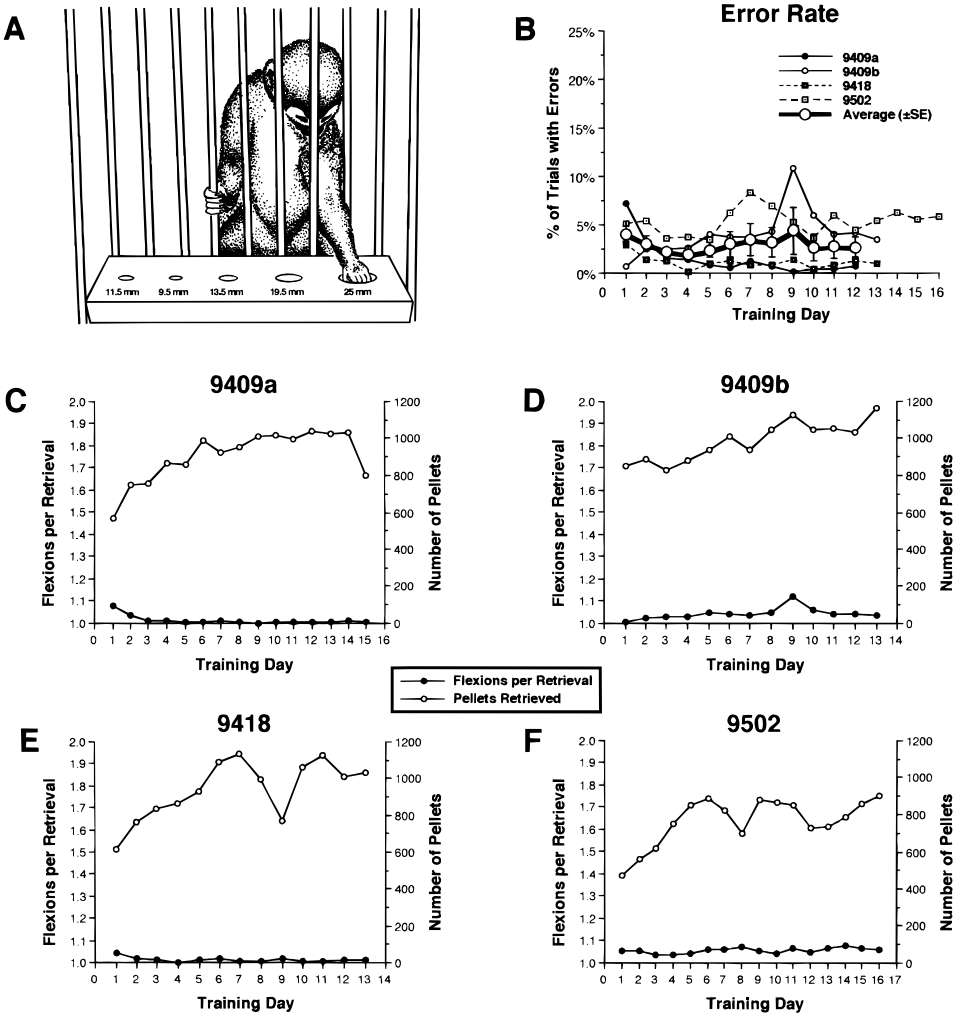


FIG. 3. Summary of task performance measures. (A) Depiction of a squirrel monkey performing the large-well pellet retrieval task. Note the relative simplicity of the task due to the size of the training well compared to the size of the hand. (B) Graph of daily error-rate values for each subject and the average error-rate for the group. Average error-rate is illustrated with the thick solid line. Average values were calculated only for days with available data for all four subjects. (C–F) Graphs of daily retrieval efficiency (flexions/retrieval) and number of retrieved pellets for each subject.

strategies. Further, the relative use of these strategies could have been strongly stereotyped or highly variable throughout the training period. Because a variable or inconsistent retrieval strategy might fail to produce systematic alterations in motor maps, videotaped trials were examined frame-by-frame to identify the specific movement patterns used to extract a pellet from the training well during four epochs of training.

At a gross behavioral level, each of the four subjects adopted a consistent body position with respect to the Klüver board, although the exact position varied somewhat for each animal. Typically, monkeys oriented themselves in front of the board, centering their bodies slightly to one side of the training well to allow the preferred retrieval hand to have direct access to the well (see Figs. 2 and 3A). Retrievals were performed by reaching

through the cage bars with the preferred hand only and directing it toward the food well. Once the pellet was grasped and extracted from the well, the hand was returned to the cage, typically via a shoulder retraction, an elbow flexion, or both, and the pellet was consumed. Variations from this general motor strategy were rarely, if ever, observed.

Frame-by-frame microanalysis of the movement patterns used revealed that, for every trial observed, monkeys used at least two different movements of the distal forelimb to perform the pellet extraction. Thus, every movement pattern described in this study was composed of at least two individual movements. In addition, it was found that monkeys used a variety of different movement patterns to extract pellets from the large well, for a group total of nine distinct movement patterns (P1–P9, Table 2). However, two of the

TABLE 2
Pellet Extraction Movement Patterns: Percentage Use per Epoch

Movement pattern		9409a				9409b				9418				9502			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
	Epoch No.																
P1	Finger flexion, forearm supination	81	58	30	40	82	55	53	51	26	44	40	45	63	43	44	39
P2	Finger flexion + forearm supination	10	35	60	43	10	38	35	33	63	49	53	43	15	53	36	49
P1 + P2	Total: preferred patterns	92	93	90	83	93	93	88	85	89	92	93	88	78	95	80	87
P3	Finger flexion, forearm supination + wrist extension	5	0	0	0	8	0	0	8	—	—	—	—	5	0	3	3
P4	Finger flexion, forearm supination + wrist radial	0	3	3	5	—	—	—	—	0	0	3	5	3	0	3	0
P5	Finger flexion + wrist radial, forearm supination	0	5	3	3	0	5	10	3	3	8	5	5	3	3	5	5
P6	Finger flexion + wrist ulnar, forearm supination	—	—	—	—	—	—	—	—	—	—	—	—	3	0	0	0
P7	Finger flexion + wrist extension, forearm supination	3	0	5	10	0	0	3	3	—	—	—	—	5	3	10	5
P8	Finger flexion + wrist flexion, forearm supination	—	—	—	—	0	3	0	3	8	0	0	3	3	0	0	0
P9	Finger flexion + forearm pronation, forearm supination	—	—	—	—	—	—	—	—	—	—	—	—	3	0	0	0
P3–9	Total: nonpreferred patterns	8	8	10	18	8	8	13	15	11	8	8	13	23	5	20	13

Note. Percentage values were individually rounded to the nearest whole number, resulting in some totals not equaling 100%. In the first column, a *comma* indicates two movements in sequence and a *plus sign* indicates two movements in combination; in the remaining columns, a *dash* indicates a movement pattern that was never observed for a given animal.

nine observed patterns were used with much greater frequency than the others, namely finger flexion/forearm supination sequence (P1) and finger flexion/forearm supination combination (P2). It should be noted that these two preferred patterns differed only in the relative timing of their component movements (e.g., Fig. 2). For each animal, the two preferred patterns were used in greater than 80% of the trials (mean $88.4 \pm 3.3\%$, averaged for all animals over all epochs). Combined use of the two preferred patterns (P1 + P2, see Fig. 4) remained stable over the four epochs for each individual animal ($p > .05$, one-way ANOVA; Figs. 4A–4D) and for the entire group ($p = .259$, one-way ANOVA; Fig. 4E). Interestingly, the component movements of the two preferred patterns (finger flexion, forearm supination) were also used as component movements in all of the other observed movement patterns (Table 2). Thus, both a finger flexion movement and a forearm supination movement occurred in 100% of the trials examined, but were accompanied by additional movements in an average of only 11.6% of the trials.

The relative use of finger flexion/forearm supination movements as a sequence (i.e., P1) versus as a combination (i.e., P2) during pellet extraction varied over the course of training for each animal (Fig. 4). For three subjects (9409a, 9409b, 9502), use of P1

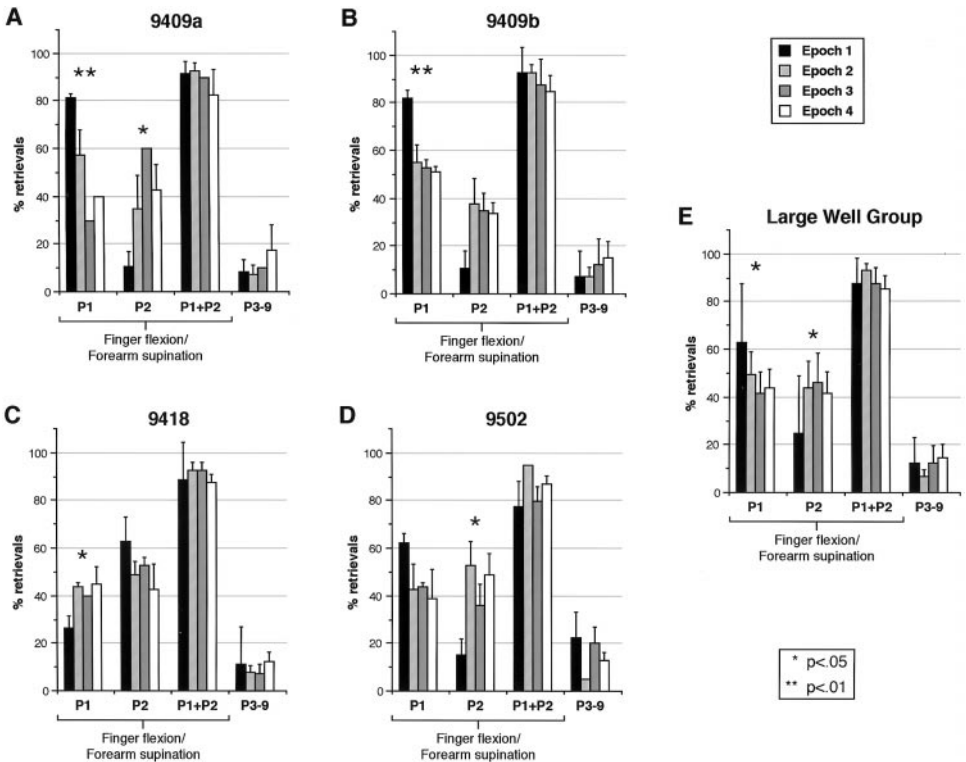


FIG. 4. Summary of movement patterns used during large-well training for each subject (A–D) and averaged for the entire group (E). The first three categories (x-axis) on each graph refer to the preferred finger flexion/forearm supination movement patterns, while the fourth category (“Other”) refers to the sum of all the remaining observed movement patterns (as listed in Table 2). Error bars equal one standard deviation. Data in A–D are the average of the percentage use values from the morning and afternoon training sessions for each epoch. Data in E are the average of the percentage use values from eight training sessions (two per subject) for each epoch. Each epoch represents one training day per subject, as follows: 9409a (days 1, 4, 7, and 10), 9409b (1, 5, 9, 13), 9418 (1, 6, 9, 13), and 9502 (1, 5, 11, 16) for epochs 1–4, respectively.

tended to decrease and P2 use tended to increase as training proceeded (Figs. 4A, 4B, and 4D). In contrast, one subject (9418) showed the opposite tendency, using P1 more frequently and P2 less frequently over time (Fig. 4C). These changes were statistically reliable in three subjects for P1 and two subjects for P2 ($p < .05$, one-way ANOVA; see Fig. 4) and nearly reliable in a third subject for P2 (9409b, $p = .066$, one-way ANOVA). The greatest variation occurred between the first and the second epochs in three subjects (9409b, 9418, 9502) for both P1 and P2. Post hoc tests revealed that frequency of use of P1 and P2 after epoch 1 remained stable for every comparison except P1 use in 9409a ($p < .05$ for epochs 2–3 and 2–4, Fisher's PSLD). On the whole, the large-well training group (Fig. 4E) showed a statistically reliable tendency to use P1 less frequently over time ($p = .025$, one-way ANOVA) and to use P2 more frequently over time ($p = .020$, one-way ANOVA). Post hoc analysis revealed no differences between epochs 2 through 4; only epoch 1 was reliably different from the other epochs ($p < .05$, Fisher's PSLD).

Speed (latency) of pellet retrieval. In addition to analyzing the movements used during the task on selected trials, three measures of pellet retrieval latency (latency to extract, LE; latency to retract, LR; latency to retrieve, LT) were recorded on these trials. Latency results are illustrated in Fig. 5. It was found that all three latency measures decreased as training proceeded for each of the four subjects ($p < .01$, one-way ANOVA; see Fig. 5) and for the group as a whole ($p < .0001$, one-way ANOVA). The greatest latency decreases

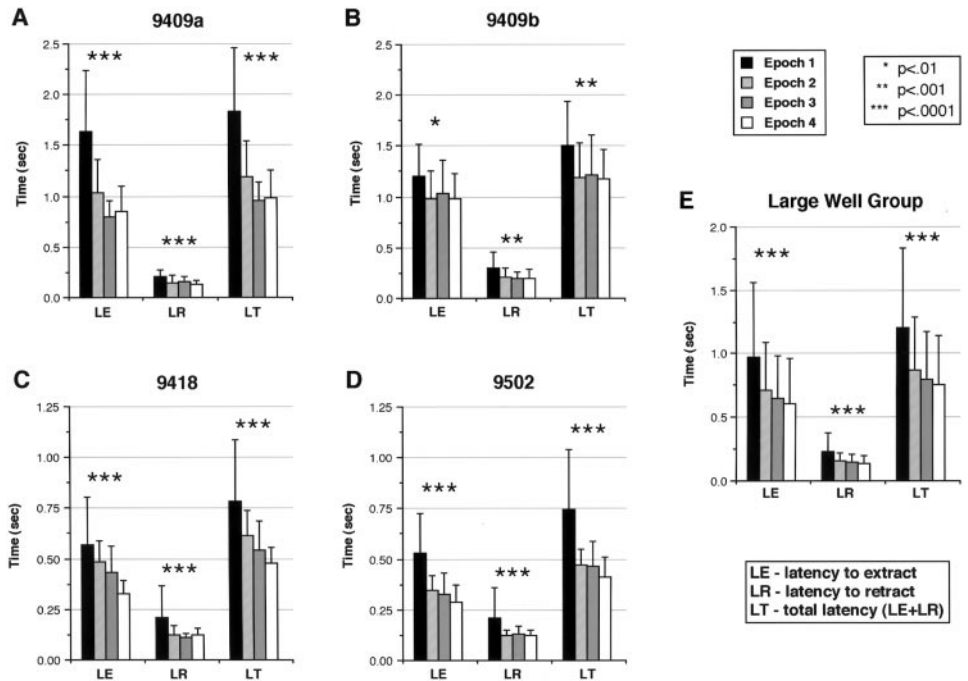


FIG. 5. Speed of pellet retrievals during large-well training for each subject (A–D) and averaged for the entire group (E). There was a consistent increase in speed between epochs 1 and 2 for all subjects and for all latency measures. Subject 9409b had a smaller change in latency than subject 9409a (note: same animal), suggesting that some aspects of the previous training experience may have been retained during the intervening 6 months. Error bars equal one standard deviation. Data in A–D represent the average latency for all trials in the given epoch (i.e., up to 40 trials; see Materials and Methods). Data in E are the average of all trials across all animals for the given epoch (i.e., up to 160 trials/epoch).

occurred between epochs 1 and 2 in every instance. In fact, motor behavior during epoch 1 was significantly slower than during any other epoch of training for all three latency measures (individually, $p < .05$ or less, for the group, $p < .0001$, Fisher's PLSD). Latency differences were less pronounced between the remaining epochs. Only two subjects showed any further reliable decreases in latency after epochs 1–2 (9409a, $p < .05$ for LE and LT epochs 2–3 and 2–4, Fisher's PLSD; 9418, $p < .01$ for LE epochs 2–4 and 3–4 and $p < .001$ for LT epochs 2–4, Fisher's PLSD). For the group, there was one additional significant decrease in latency ($p < .05$ for LE and LT epochs 2–4, Fisher's PLSD). Interestingly, after the initial decrease (epochs 1–2), LR remained stable for the remainder of the training period for all four subjects and for the group. Thus, any reliable decreases in latency after epochs 1–2 were found only for LE and LT.

To evaluate whether there was any relationship between the shift in the relative use of P1 and P2 (see previous section) as training proceeded and the overall increase in retrieval speed (above), average latencies (pooled across all epochs) were calculated separately for P1 and P2. As shown in Fig. 6, for the three subjects that used P2 more frequently as training proceeded (9409a, 9409b, 9502), it was found that P2 was performed faster than P1 (average for all three subjects: LE, 947 ms vs 672 ms; LR, 198 ms vs 145 ms; LT, 1145 ms vs 817 ms; P1 vs P2, respectively). These differences were statistically significant for each animal and each latency measure ($p < .05$, unpaired t test, two-tailed). In contrast, subject 9418, who used P1 more frequently as training proceeded, performed P1 slightly faster than P2 (average: LE, 454 ms vs 466 ms; LR, 132 ms vs 156 ms; LT, 587 ms vs 621 ms; P1 vs P2, respectively), although these differences were not statistically reliable ($p > .05$, unpaired t test, two-tailed).

Neurophysiological Results

In the preceding section, various aspects of the motor behavior exhibited by monkeys performing the large-well retrieval task were described. In this section, the organization of movement representations in M1 before and after training on the large-well task are examined, with specific emphasis on whether any areal differences exist between these two representational maps. This analysis will be used to address the question of whether

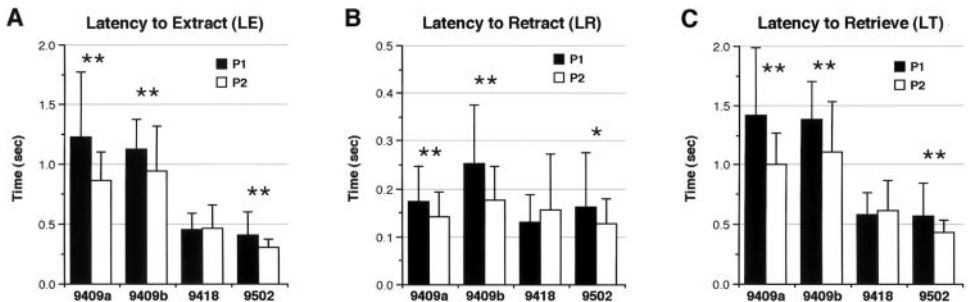


FIG. 6. Differences in speed between finger flexion/forearm supination sequences versus combinations. (A–C) Graphs of each latency measure averaged across all four epochs for each subject. Error bars equal one standard deviation. For every latency measure, the difference between sequence speed and combination speed was significant for 9409a, 9409b, and 9502. There were no significant differences found for 9418. * $p < .05$; ** $p < .01$.

repetitive motor use, as performed during large-well training, can induce alterations in the organization of M1 motor maps.

Features of ICMS-derived motor maps. Motor maps in M1 were qualitatively similar to other recently described ICMS mapping results in nonhuman primates (Donoghue, Leibovic, & Sanes, 1992; Gould, Cusick, Pons, & Kaas, 1986; Huntley & Jones, 1991; Nudo et al., 1992, 1996; Schieber & Deuel, 1997; Schieber & Hibbard, 1993; Waters, Samulack, Dykes, & McKinley, 1990). Briefly, movements around individual joints could be evoked by stimulation with low current levels (less than 30 μA), with an average threshold for all responsive sites of $20.8 \pm 8.2 \mu\text{A}$. At many sites, increasing the current intensity above threshold levels resulted in additional evoked movements around other joints. Evoked movements were exclusively contralateral to the stimulated hemisphere, except for anatomically constrained bilateral movements of the lower jaw and trunk. No purely ipsilateral movements were observed.

The representation of the distal forelimb, also referred to as the hand representation, was composed of finger, thumb, wrist, and forearm movements, arranged in a complex, mosaical pattern (e.g., Fig. 1C). These distal representations were typically surrounded on three sides (medial, rostral, lateral) by more proximal movements, such as elbow and shoulder movements, as well as occasional axial/trunk movements medially and face movements laterally. Caudally, the map was bounded by a nonresponsive region from which no movements could be evoked up to 30 μA .

These general organizational features were not noticeably altered by either the control procedures or the motor training procedures used in this study.

Control group—ICMS mapping. For brevity, mapping data from the control group are not discussed in detail in this article, but are summarized in Table 3. We have previously demonstrated that representational areas in control maps do not appear to change in any systematic manner over time (Milliken et al., 1994, 1995; Nudo et al., 1996). Typically, only very small, statistically insignificant variations in individual representational areas relative to the representation of the total distal forelimb were found. For example, in control subjects, the mean digit area comprised 54.74% of the pretraining map (map1) and 54.68% of the posttraining map (map2) and the mean wrist/forearm area comprised 36.06% of map1 and 34.62% of map2 (see Table 3). Since these control maps provide an estimate of the normal variability present in ICMS-derived motor maps, we used these data in statistical comparisons with the large-well training group in order to clarify which map alterations, if any, could be reliably attributed to the motor training procedure.

Effects of large-well training on motor map organization. Three organizational features of representational maps were examined for possible alterations following the experimental manipulations: topographic organization of the map, overall size of the map, and the relative size of the individual representations that compose the map. The effects of large-well training on each of these features will be discussed below.

Figure 7 illustrates pre- and posttraining maps from the four training experiments in this study. With regard to the topographic organization of these maps, two qualitative observations can be made. First, despite idiosyncratic features in individual monkeys, the overall shape of the map remained largely unchanged after training. For example, in both maps for subject 9502, the hand representation was narrow caudally, but was wider

TABLE 3
M1 Movement Representation Data

Movement category	Percentage Distal forelimb area (mean \pm SD)							ANOVA results	
	Large-well training group			Control group			<i>F</i>	<i>p</i>	
	Map 1	Map 2	Change	Map 1	Map 2	Change			
Distal forelimb area (not % area)	7.85 \pm .80	7.24 \pm 1.20	-0.61 \pm 0.60	12.91 \pm 1.84	12.26 \pm 1.59	-0.65 \pm 1.87	.002	.969	
Digit	40.04 \pm 20.05	39.51 \pm 20.43	-0.53 \pm 2.77	54.74 \pm 10.31	54.68 \pm 13.05	-0.06 \pm 3.44	.038	.852	
Wrist/forearm	54.08 \pm 17.06	56.06 \pm 18.95	1.97 \pm 4.40	36.06 \pm 6.11	34.62 \pm 9.18	-1.44 \pm 6.53	.787	.409	
Digit + Wrist/forearm*	2.44 \pm 1.10	2.14 \pm 1.14	-0.30 \pm 0.11	6.28 \pm 3.39	5.82 \pm 3.73	-0.46 \pm 2.32	.025	.881	
Wrist/forearm + Proximal	3.27 \pm 2.13	1.58 \pm 1.38	-1.69 \pm 1.44	1.31 \pm 2.05	2.41 \pm 1.54	1.10 \pm 1.02	6.687	.041	
Digit, inclusive	42.64 \pm 18.83	42.36 \pm 19.58	-0.28 \pm 3.17	62.20 \pm 7.27	62.97 \pm 10.19	0.77 \pm 5.59	.114	.747	
Wrist/forearm, inclusive	59.49 \pm 20.40	59.82 \pm 20.47	0.33 \pm 2.73	44.08 \pm 9.21	42.85 \pm 12.54	-1.23 \pm 4.11	.376	.562	
Finger	31.82 \pm 13.89	29.43 \pm 10.91	-2.39 \pm 4.33	36.53 \pm 5.26	38.68 \pm 7.76	2.15 \pm 6.66	1.289	.300	
Thumb	8.22 \pm 7.05	10.05 \pm 10.26	1.84 \pm 6.23	18.15 \pm 8.52	15.85 \pm 6.43	-2.30 \pm 4.00	1.547	.260	
Wrist*	44.55 \pm 16.66	51.29 \pm 18.62	6.74 \pm 5.99	25.25 \pm 7.01	28.40 \pm 6.52	3.15 \pm 7.26	.417	.542	
Forearm	9.56 \pm 8.38	5.17 \pm 6.50	-4.39 \pm 2.02	10.83 \pm 4.81	6.18 \pm 3.62	-4.64 \pm 4.96	.300	.604	
Finger + Wrist/forearm	0.84 \pm 1.15	1.57 \pm 1.36	0.73 \pm 0.59	4.08 \pm 3.29	3.10 \pm 2.35	-0.99 \pm 3.03	1.246	.307	
Wrist + Digit	1.48 \pm 1.62	1.77 \pm 1.26	0.29 \pm 0.58	4.45 \pm 3.26	4.24 \pm 2.72	-0.20 \pm 2.95	.045	.840	
Finger, inclusive**	32.83 \pm 13.22	31.43 \pm 10.03	-1.39 \pm 4.16	41.36 \pm 7.62	43.28 \pm 7.04	1.92 \pm 9.87	.378	.561	
Thumb, inclusive	9.82 \pm 6.74	10.90 \pm 10.59	1.09 \pm 6.40	20.50 \pm 8.07	19.74 \pm 5.53	-0.76 \pm 5.63	.046	.838	
Wrist, inclusive**	49.30 \pm 18.78	54.27 \pm 19.76	4.97 \pm 4.89	30.11 \pm 8.53	34.65 \pm 8.30	4.54 \pm 6.96	.001	.977	
Forearm, inclusive	10.52 \pm 9.63	5.91 \pm 7.95	-4.61 \pm 1.89	14.01 \pm 7.47	8.36 \pm 5.89	-5.65 \pm 5.63	.232	.647	
Finger flexion	14.06 \pm 11.40	14.17 \pm 8.77	0.10 \pm 3.33	16.50 \pm 4.34	14.38 \pm 5.72	-2.13 \pm 2.90	1.880	.219	
Finger extension	12.22 \pm 11.20	9.22 \pm 7.36	-3.00 \pm 4.04	15.93 \pm 8.16	20.47 \pm 14.14	4.54 \pm 6.82	2.163	.192	
Thumb flexion	2.13 \pm 3.20	1.75 \pm 2.43	-0.38 \pm 3.42	2.59 \pm 1.89	2.34 \pm 2.32	-0.26 \pm 1.68	.004	.950	
Thumb extension	5.72 \pm 4.79	7.51 \pm 6.96	1.79 \pm 2.92	13.78 \pm 6.35	11.67 \pm 2.61	-2.11 \pm 4.93	2.170	.191	
Wrist extension	12.58 \pm 5.50	12.19 \pm 3.12	-0.38 \pm 2.85	9.00 \pm 3.79	10.09 \pm 3.94	1.09 \pm 7.19	.116	.743	
Wrist radial*	26.34 \pm 21.85	31.91 \pm 24.82	5.57 \pm 6.08	7.59 \pm 6.98	8.56 \pm 8.23	0.97 \pm 1.72	1.873	.220	

Wrist ulnar	5.47 ± 8.51	6.63 ± 13.25	1.16 ± 4.91	7.01 ± 6.73	8.28 ± 8.64	1.28 ± 2.09	1.125	.330
Forearm supination	9.39 ± 8.06	4.97 ± 6.11	-4.43 ± 2.09	7.93 ± 5.24	4.44 ± 2.01	-3.49 ± 5.71	.616	.462
Finger flexion, inclusive	15.07 ± 10.43	15.70 ± 8.19	0.62 ± 2.83	18.89 ± 5.91	16.38 ± 6.31	-2.51 ± 5.03	1.761	.233
Finger extension, inclusive	12.22 ± 11.20	9.70 ± 7.55	-2.52 ± 4.09	17.28 ± 7.92	21.91 ± 15.19	4.63 ± 7.70	1.288	.300
Thumb flexion, inclusive	2.13 ± 3.20	1.75 ± 2.43	-0.38 ± 3.42	2.59 ± 1.89	2.85 ± 2.33	0.26 ± 1.62	.236	.644
Thumb extension, inclusive	7.32 ± 4.69	8.08 ± 6.82	0.76 ± 2.64	16.11 ± 6.74	16.25 ± 2.84	0.14 ± 5.69	<.001	.987
Wrist extension, inclusive	15.18 ± 7.42	14.77 ± 3.65	-0.41 ± 4.18	13.10 ± 5.34	14.60 ± 2.00	1.50 ± 7.14	.207	.665
Wrist radial, inclusive*	28.28 ± 23.74	32.30 ± 25.27	4.02 ± 5.70	7.81 ± 7.13	9.00 ± 9.09	1.20 ± 2.34	.768	.415
Wrist ulnar, inclusive	5.66 ± 8.90	6.63 ± 13.25	0.97 ± 4.54	3.78 ± 2.37	4.26 ± 2.27	0.48 ± 0.40	.188	.679
Forearm supination, inclusive	10.35 ± 9.31	5.71 ± 7.56	-4.64 ± 1.95	9.76 ± 6.59	5.82 ± 3.66	-3.94 ± 6.95	.542	.489
Finger flexion/extension*	26.28 ± 16.37	23.39 ± 12.82	-2.89 ± 4.46	32.43 ± 7.83	34.85 ± 11.54	2.42 ± 6.56	1.320	.294
Finger flexion + Wrist extension*	0.20 ± 0.40	0.90 ± 0.77	0.70 ± 0.48	1.87 ± 2.30	0.92 ± 0.65	-0.95 ± 2.25	1.610	.251

Note. Data reported only for categories submitted to statistical comparison (i.e., 35 categories). **Boldface italics** indicate significant ANOVA ($p < .05$) results for large-well training group (versus control). Symbols in the first column indicate significant statistical categories for small-well training group (* $p < .05$ and ** $p < .07$; from Nudo et al. (1996)).

LARGE WELL TRAINING CASES: DISTAL FORELIMB MOVEMENT REPRESENTATIONS

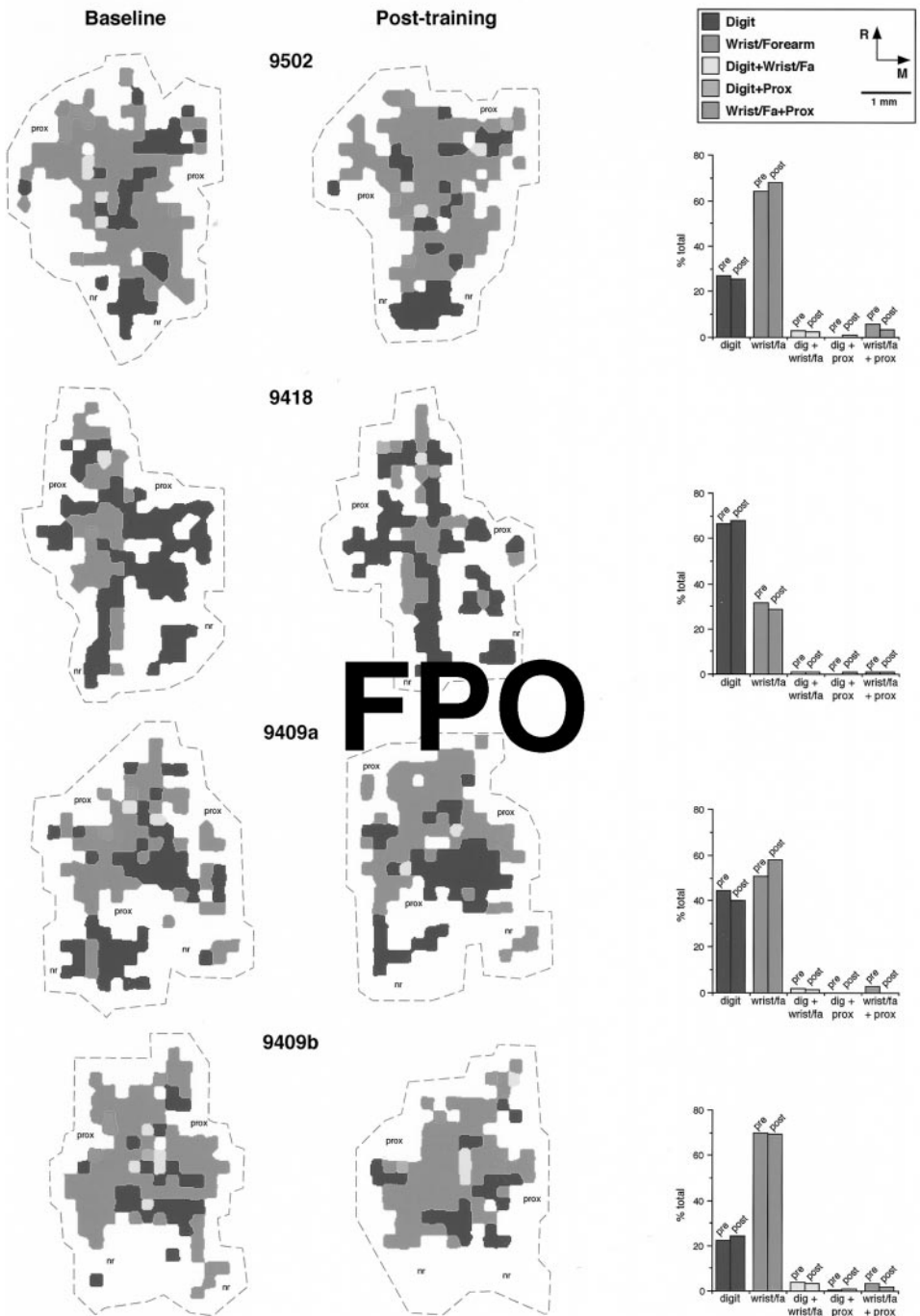


FIG. 7. Maps of M1 distal forelimb representations for each subject before (**left**) and after (**middle**) training on the large-well task. For this illustration, movements are broadly classified as digit (red), wrist or forearm (green), digit + wrist/forearm dual-response (yellow), digit + proximal dual-response (light blue), and wrist/forearm + proximal dual-response (purple) movements. Each colored square in the maps corresponds to a single electrode penetration. Dashed lines indicate the extent of the explored cortical territory. Proximal (prox) and nonresponsive (nr) sites have been omitted for clarity. Bar graphs (**right**) indicate the percentage of the hand area occupied by the five illustrated representations for each map.

rostrally. In addition, the physical location of the hand representation relative to the surface vasculature did not change after training (not illustrated). It should be noted that there were some local, site-to-site variations in movement representations between the pretraining and the posttraining maps, similar to the variations seen in control maps (Nudo et al., 1996), suggesting that this reflects a normal organizational feature of maps of motor representations derived using the ICMS technique.

The overall size of the distal forelimb representation was calculated for each animal, before and after training. Although the mean representational area for the training group decreased slightly from 7.85 to 7.24 mm², an average change of 8.1%, this difference was not statistically significant ($p = .969$, compared to controls, one-way ANOVA; Table 3) and was within the range of variance in control procedures in previous studies from this laboratory (Nudo et al., 1992, 1996). Since maps across individual animals can differ widely in absolute size (Nudo et al., 1992), areal data from the remaining movement categories were normalized as a percentage of total distal forelimb area (“percentage area”) for statistical testing, thereby reducing the variance introduced by using absolute area measurements (Nudo et al., 1996).

Based on a previously described movement classification system (Nudo et al., 1992), ICMS-evoked movement data were coded into 87 separate movement categories for each map (eight training maps, eight control maps). Categories comprising less than 2% of the total distal forelimb area were eliminated from statistical analysis. As in previous studies (Nudo et al., 1996), this was done to exclude categories that were infrequently observed and may not be biologically significant. One exception to this criterion was made for the finger flexion + wrist extension dual-response category. In our previous study of small-well training (Nudo et al., 1996), this category exceeded 2% of the total hand area and was found to correlate with learned changes in retrieval motor behavior (see below). Thus, we included the category in the present study in order to facilitate comparison with our previous results. After this 2% exclusion criterion was applied, 35 movement categories remained for statistical analysis (summarized in Table 3).

In general, there were *no systematic changes in the areal extent of distal forelimb movement representations in MI following repetitive motor training on the large-well task*. In Fig. 7, for example, bar graphs indicate that the percentage of the map composed of digit, wrist/forearm, and dual-response representations remained quite stable for each subject; in almost every category, there was less than a 4% difference in representational area between map1 and map2. For the entire training group, the mean digit representation decreased from 40.04% in map1 to 39.51% in map2, a difference of 0.53%, while the wrist/forearm representation increased from 54.08% in map1 to 56.06% in map2, a difference of 1.97%. These changes were statistically insignificant and comparable in magnitude to controls (Table 3). In fact, of the 35 movement categories subjected to statistical analysis, only one category (wrist/forearm + proximal dual-response) showed a small but statistically reliable difference between the pretraining and the posttraining maps ($p = .041$, repeated-measures ANOVA, Table 3). This representation decreased from 3.27% (map1) to 1.58% (map2) following large-well training, a difference of 1.69%.

For the finger flexion + wrist extension category, the large-well training group showed an increase in representation from 0.20% (map1) to 0.90% (map2), a difference of 0.70%, while the controls decreased from 1.87% (map1) to 0.92% (map2), a difference of 0.95% (Table 3). These changes were not significantly different from each other ($p = .251$,

repeated-measures ANOVA). In our earlier study of small-well training effects, the training group showed an increase from 1.55% (map1) to 4.21% (map2), a difference of 2.66%, and differed significantly from controls ($p = .019$, repeated-measures ANOVA; see Nudo et al., 1996). Categories that showed significant ($n = 6$) or near-significant ($n = 2$) differences from controls in the small-well study are indicated in Table 3. Note that none of these eight categories differed from controls after large-well training.

DISCUSSION

This study has demonstrated that the behavior of squirrel monkeys trained on a repetitive, large-well retrieval task was highly successful, stereotyped, and consistent, with only very subtle changes in behavior over time. Further, this form of motor behavior had no systematic effects on the representations of distal forelimb movements in primary motor cortex (M1). The significance of these findings is discussed in the following sections.

Features of Behavioral Adaptation—Evidence of Motor Learning?

The large-well retrieval task was intended to promote consistent motor activity in the absence of motor skill acquisition. The relatively large size of the well permitted monkeys to perform pellet retrievals using a prehensile type of grasping behavior. Prehensile grasping is characterized by the absence of independent digit control; digit movements are made in an all-or-none fashion. Squirrel monkeys typically use a prehensile grip when grasping objects and rarely, if ever, use a precision grip (Fragaszy, 1983). Thus, this retrieval task was well suited to the natural motor abilities of squirrel monkeys and as such should not have required any additional motor skills to perform.

Further, several measures of the subjects' motor behavior suggest that retrieval strategy was optimized early in training and remained unchanged over time. For example, the relative ease of the task, as indicated by the initial values for retrieval efficiency and error-rate, suggests that there was no particular driving force for the development of new motor skills or strategies during task performance. Also, the combined use of P1 (sequential use of finger flexion and forearm supination) and P2 (combinational use of finger flexion and forearm supination) to perform pellet extractions was highly stereotyped on the first day of training and remained unchanged throughout the training period. This consistency of movement strategy further suggests that motor skill acquisition did not occur.

Some behavioral measures, including retrieved pellet number, the relative frequency of use of P1 and P2, and the speed of retrieval movements, did change during the training period. These changes occurred early in the training period and remained essentially stable thereafter. Increases in pellet number were almost certainly related to the overall increase in retrieval speed within individual trials (e.g., Fig. 5) and to a concurrent reduction in delay time between the completion of one trial and the start of the next trial (anecdotal observation). Furthermore, it seems probable that the change in frequency of use of P1 and P2 was also related to changes in movement speed (e.g., Fig. 6).

Although a general sense of what is meant by "motor skill" exists among researchers, there is no general agreement regarding what constitutes the acquisition of motor skill. Relevant to the present discussion is whether or not changes in movement speed, in the absence of any other changes in behavioral measures, are evidence of skill learning. In

our view, motor skill learning is operationally defined as a change in motor behavior, specifically referring to the increased use of novel, task-specific joint sequences and combinations, resulting from practice and/or repetition. We do not include changes in speed as criteria, as they may occur as a function of motivational state, also called dispositional learning (e.g., Amsel, 1992). Thus, we conclude that no motor skill learning occurred during the large-well retrieval task. Others have argued that changes in the speed of movement, if not accompanied by reciprocal changes in the accuracy of movement, indicate skill learning (e.g., Fitts, 1954; Hallett, Pascual-Leone, & Topka, 1996). Even if this definition of motor learning is accepted, and it is then concluded that motor skill learning did occur during the large-well retrieval task, the present data still suggest that changes in motor skills related to the *speed* of movement are not reflected in M1 representations and that plasticity of these representations is driven only by changes in motor skills related to the *pattern* of movement.

Stability of M1 Motor Maps Following Motor Training

In general, there were no systematic, task-related changes in movement representations following training on the large-well task. The only reliable difference (wrist/forearm + proximal dual-response representations) was primarily due to a decrease in wrist + proximal representations. While proximal joint movements were not evaluated, overt wrist movements were observed very infrequently during pellet extraction, suggesting that wrist/proximal movement combinations rarely, if ever, occurred during large-well training. Although it is tempting to relate infrequent use to decreases in representational area, the area of numerous other infrequently observed movement patterns did not decrease following training. Alternatively, since the behavioral data were based on videotape analysis, it is possible that unobservable wrist stabilization activity occurred during the trained movements. If so, wrist/forearm + proximal representations might have decreased in size due to less wrist stabilization after large-well training. Still, less stabilization might be expected to result in more frequent overt wrist movements after training, which was not detected. Thus, this result should be viewed with caution as it may not reflect an experimentally relevant effect.

The observation of changes in behavior early in training suggests the possibility that motor maps may have undergone transient changes and then returned to baseline conditions before the posttraining map was derived. In our previous study of small-well training (Nudo et al., 1996), posttraining maps were derived within 3 to 4 days of asymptotic performance on the task (as defined by stable efficiency values; Fig. 8A). Reliable task-related map changes were still detected after that period of time. In the present study, posttraining maps were derived 7 days or more after reaching asymptotic performance (as suggested by latency measures, since efficiency never varied; Figs. 3 and 5). Karni and colleagues have found that task-related changes in functional activity can persist in M1 for months following the acquisition of a new motor skill, even without any additional practice on the skill (Karni, Meyer, Rey-Hipolito, Jezzard, Adams, Turner, & Ungerleider, 1998). Further, some changes in functional activity have been shown to occur within a single experimental session, although there is conflicting evidence regarding whether or not these short-term changes can persist for any substantial length of time (Classen, Liepert, Wise, Hallett, & Cohen, 1998; Karni et al., 1998; Pascual-Leone et al., 1994;

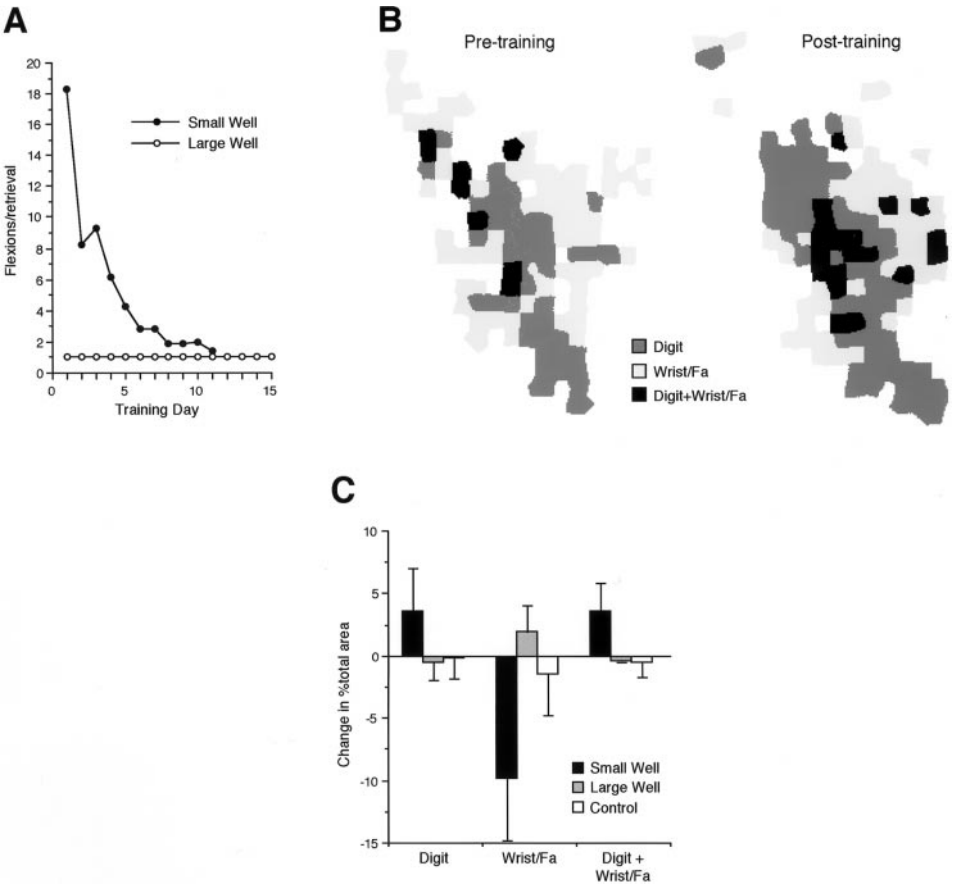


FIG. 8. Summary of the effects of small-well training on M1 motor maps. **(A)** Comparison of retrieval efficiency data for a small-well training subject (8704) and a large-well training subject (9409a). Monkeys trained on the small well showed a clear improvement in efficiency over time, concurrent with the development of a stereotypical movement pattern for pellet retrieval (not illustrated), suggesting the acquisition of a new motor skill. **(B)** Motor maps derived before (**left**) and after (**right**) small-well training (subject 9202). Note the clear changes in representational areas for the three illustrated categories (e.g., expansion of digit and digit + wrist/forearm representations) in contrast to the relative stability of maps presented in Fig. 7. For grayscale clarity, digit + proximal representations were shaded as digit representations (dark gray) and wrist/forearm + proximal representations were shaded as wrist/forearm representations (light gray). **(C)** Comparison of changes in percentage area for the representations illustrated in **B**. In the small-well study, reliable expansions of digit and digit-related representations occurred, paralleling the development of new movement patterns involving coordinated digit use. Note that changes for the small-well group ($n = 3$) were substantially larger than those for the large-well ($n = 4$) or control ($n = 4$) groups and that the magnitude of changes for the large-well group were comparable to that of controls. Error bars equal one standard deviation. Data for the small-well group were adapted from Nudo et al. (1996).

Zhuang et al., 1998). Thus, although it seems likely that any experience-driven changes in M1, if present during large-well training, would have persisted under the conditions used in this study, the possibility of transient map changes cannot be completely discounted based on the available data.

A variable or inconsistent motor strategy might fail to produce reliable changes in motor maps. However, since monkeys almost exclusively used only two movements

(finger flexion and forearm supination) consistently throughout the training period, the absence of map changes probably cannot be attributed to behavioral variability. Furthermore, using neurophysiological techniques identical to those described in the present study, small-well retrieval training resulted in reliable, task-related changes in M1 representations (Nudo et al., 1996), suggesting that the absence of map changes following large-well training probably cannot be attributed to procedural or methodological differences.

Although the only task difference between small-well and large-well training was the size of the training well, monkeys in the two groups demonstrated substantially different behavioral and neurophysiological results. Figure 8 provides a brief summary of the results of the small-well training study by Nudo et al. (1996) in comparison to the present results. Due to the size of the training well (9.5-mm diameter), monkeys in the small-well training group could insert only one or two fingers into the well for use during pellet retrieval. Monkeys performing small-well retrievals became increasingly more efficient between initial training sessions (flexions/retrieval typically >5.0) and final training sessions (flexions/retrieval typically near 1.5; Fig. 8A). Concurrently, their pellet retrieval strategy changed from the use of several unsuccessful patterns to the stereotyped use of a single, more successful pattern (Friel & Nudo, 1998; Nudo et al., 1996). Specific representations of movements involved in the successful retrieval pattern expanded following training (e.g., Figs. 8B and 8C). For example, the representation of finger flexion and finger extension movements, which were critically involved in correct placement of the fingers into the well, increased by 13.1% (33.1 to 46.2%, $p < .05$), and the representation of finger flexion + wrist extension dual-response movements, which comprised the successful movement pattern used at the end of the training period, expanded by 2.7% ($p < .05$) (see Nudo et al., 1996). Thus, as monkeys acquired a new motor skill, indicated by the emergence of a new retrieval movement pattern in parallel with improvements in retrieval efficiency, the corresponding cortical representations reorganized to reflect this skill acquisition.

Representational Plasticity in M1—Use-Dependent or Learning-Dependent?

It is now generally held that behavioral experience can result in the modification of cortical maps (Kaas, 1991; Merzenich et al., 1988; Ungerleider, 1995; Weinberger, 1995). This concept is often referred to as the “*use-dependent*” hypothesis, in reference to the presumptive relationship between the use or activity of specific sensory inputs or motor outputs and specific changes in cortical maps resulting from this use. Almost all studies of this type involve repetitive behaviors to produce the observed neural plasticity (e.g., Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Jenkins, Merzenich, Ochs, Allard, & Guíc-Robles, 1990; Pascual-Leone & Torres, 1993). Several studies have suggested additionally that the coordinated timing of neural activity may be a crucial determinant of representational plasticity (e.g., Ahissar, Vaadia, Ahissar, Bergman, Arieli, & Abeles, 1992; Allard, Clark, Jenkins, & Merzenich, 1991; Cohen, Gerloff, Ikoma, & Hallett, 1995; Recanzone, Merzenich, Jenkins, Grajski, & Dinse, 1992; Singer, 1995; Wang, Merzenich, Sameshima, & Jenkins, 1995).

The present study demonstrates that not all repetitive behavioral experiences result in cortical map modifications. The large-well retrieval task promoted consistent, intensive use of a limited set of movements, specifically finger flexion and forearm supination, in

all four training subjects. If changes in movement representations were driven solely by repetitive use, this training procedure should have produced an expansion of the corresponding representations in M1. Further, more frequent use over time of P2 (i.e., simultaneous use of finger flexion and forearm supination movements) in three subjects should have resulted in an expansion of the corresponding dual-response representation. In fact, neither of these predicted representational changes was observed in the large-well training group, suggesting that neither motor use nor temporal contiguity alone is sufficient for producing functional reorganization in M1.

In light of these findings, we suggest that the prerequisite factor determining whether or not cortical representational plasticity occurs may be the acquisition of a novel skill (i.e., learning). A "*learning-dependent*" hypothesis of cortical plasticity predicts that if successful performance of a behavioral task involves some form of skill acquisition, whether it be a motor skill or a sensory/perceptual skill, then task-related cortical reorganization will occur. Conversely, if no skill learning occurs, then no changes in cortical maps will be observed. It should be noted that in this view of cortical plasticity, we do not exclude repetitive use and/or the contiguity of neural activity as specific guiding mechanisms for plasticity. Instead, we propose that these mechanisms do not operate to produce functional reorganization unless accompanied by skill learning.

Recent evidence from both human and animal studies tends to support this learning-dependent hypothesis of cortical reorganization (e.g., Classen et al., 1998; Cohen, Gerloff, Faiz, Uenishi, Classen, Liepert, & Hallett, 1996; Karni et al., 1995; Kleim, Lussnig, Schwarz, Comery, & Greenough, 1996; Pascual-Leone et al., 1995; Recanzone, Schreiner, & Merzenich, 1993; Wang et al., 1995; Withers & Greenough, 1989; Xerri, Coq, Merzenich, & Jenkins, 1996; Zohary, Celebrini, Britten, & Newsome, 1994). For example, in a perceptual learning paradigm, Recanzone and colleagues simultaneously presented stimuli for both an auditory and a tactile discrimination task to owl monkeys. Reorganization of somatosensory maps in area 3b occurred only when monkeys performed the tactile task and successfully made progressively more difficult discriminations over time. In contrast, no reorganization occurred in area 3b following performance of the auditory task, despite identical tactile stimulation of the hand (Recanzone et al., 1993). Thus, tactile stimuli produced cortical map plasticity only in response to the acquisition of a tactile perceptual skill. In a motor learning study, Karni and colleagues trained human subjects to perform a complex sequence of finger-to-thumb tapping movements. They found that M1 activation increased as subjects developed greater accuracy and speed on the trained sequence, compared to an untrained, activity-control sequence, suggesting that there was a learning-dependent representation of the trained sequence in M1 (Karni et al., 1995). Furthermore, Classen and colleagues found that although repetitive, unskilled movements of the thumb could produce changes in the cortical representation of thumb movement direction, these changes degraded and returned to the baseline condition within a few minutes after movement training stopped (Classen et al., 1998), supporting the hypothesis that simple motor activity is insufficient to produce long-term plasticity in cortical representations. Finally, anatomical studies of rat motor cortex have indicated that synaptogenesis and dendritic arborization are enhanced following behavioral training on a complex set of skilled motor tasks compared to unskilled, activity-matched control rats and inactive control rats (Kleim et al., 1996; Withers & Greenough, 1989). These results are particularly compelling, as they suggest that skill acquisition, but not increased use,

results in adaptive *anatomical* changes in motor cortex that may parallel learning-dependent, adaptive *physiological* changes in motor cortex.

REFERENCES

- Ahissar, E., Vaadia, E., Ahissar, M., Bergman, H., Arieli, A., & Abeles, M. (1992). Dependence of cortical plasticity on correlated activity of single neurons and on behavioral context. *Science*, **257**, 1412–1415.
- Aizawa, H., Inase, M., Mushiake, H., Shima, K., & Tanji, J. (1991). Reorganization of activity in the supplementary motor area associated with motor learning and functional recovery. *Experimental Brain Research*, **84**, 668–671.
- Allard, T., Clark, S. A., Jenkins, W. M., & Merzenich, M. M. (1991). Reorganization of somatosensory area 3b representations in adult owl monkeys after digital syndactyly. *Journal of Neurophysiology*, **66**, 1048–1058.
- Amsel, A. (1992). *Frustration theory: An analysis of dispositional learning and memory*. New York: Cambridge Univ. Press.
- Buonomano, D. V., & Merzenich, M. M. (1998). Cortical plasticity: From synapses to maps. *Annual Review of Neuroscience*, **21**, 149–186.
- Byl, N. N., Merzenich, M. M., & Jenkins, W. M. (1996). A primate genesis model of focal dystonia and repetitive strain injury. I. Learning-induced dedifferentiation of the representation of the hand in the primary somatosensory cortex in adult monkeys. *Neurology*, **47**, 508–520.
- Classen, J., Liepert, J., Wise, S. P., Hallett, M., & Cohen, L. G. (1998). Rapid plasticity of human cortical movement representation induced by practice. *Journal of Neurophysiology*, **79**, 1117–1123.
- Cohen, L. G., Gerloff, C., Faiz, L., Uenishi, N., Classen, J., Liepert, J., & Hallett, M. (1996). Directional modulation of motor cortex plasticity induced by synchronicity of motor outputs in humans. *Society for Neuroscience Abstract*, **22**, 1452.
- Cohen, L. G., Gerloff, C., Ikoma, K., & Hallett, M. (1995). Plasticity of motor cortex elicited by training of synchronous movements of hand and shoulder. *Society for Neuroscience Abstract*, **21**, 517.
- Donoghue, J. P. (1995). Plasticity of adult sensorimotor representations. *Current Opinion in Neurobiology*, **5**, 749–754.
- Donoghue, J. P., Leibovic, S., & Sanes, J. N. (1992). Organization of the forelimb area in squirrel monkey motor cortex: Representation of the digit, wrist, and elbow muscles. *Experimental Brain Research*, **89**, 1–19.
- Dykes, R. W. (1997). Mechanisms controlling neuronal plasticity in somatosensory cortex. *Canadian Journal of Physiology and Pharmacology*, **75**, 535–45.
- Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B., & Taub, E. (1995). Increased cortical representation of the fingers of the left hand in string players. *Science*, **270**, 305–307.
- Fitts, P. M. (1954). The information capacity of the human motor system controlling the amplitude of movement. *Journal of Experimental Psychology*, **47**, 381–391.
- Fragaszy, D. M. (1983). Preliminary quantitative studies of prehension in squirrel monkeys (*Saimiri sciureus*). *Brain, Behavior and Evolution*, **23**, 81–92.
- Friedman, D., Rioult-Pedotti, M.-S., & Donoghue, J. P. (1997). Motor skill acquisition strengthens horizontal connections in adult rat motor cortex. *Society for Neuroscience Abstract*, **23**, 227.
- Friel, K. M., & Nudo, R. J. (1998). Recovery of motor function after focal cortical injury in primates: Compensatory movement patterns used during rehabilitative training. *Somatosensory and Motor Research*, **15**, 173–189.
- Germain, L., & Lamarre, Y. (1993). Neuronal activity in the motor and premotor cortices before and after learning the associations between auditory stimuli and motor responses. *Brain Research*, **611**, 175–179.
- Gould, H. J., III, Cusick, C. G., Pons, T. P., & Kaas, J. H. (1986). The relationship of corpus callosum connections to electrical stimulation maps of motor, supplementary motor, and the frontal eye fields in owl monkeys. *Journal of Comparative Neurology*, **247**, 297–325.
- Grafton, S. T., Mazziotta, J. C., Presty, S., Friston, K. J., Frackowiak, R. S. J., & Phelps, M. E. (1992). Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. *Journal of Neuroscience*, **12**, 2542–48.

- Hallett, M., Pascual-Leone, A., & Topka, H. (1996). Adaptation and skill-learning: Evidence for different neural substrates. In J. R. Bloedel, T. J. Ebner, & S. P. Wise (Eds.), *The acquisition of motor behavior in vertebrates* (pp. 289–301). Cambridge, MA: MIT Press.
- Huntley, G. W., & Jones, E. G. (1991). Relationship of intrinsic connections to forelimb movement representations in monkey motor cortex: A correlative anatomic and physiological study. *Journal of Neurophysiology*, **66**, 390–413.
- Jenkins, I. H., Brooks, D. J., Nixon, P. D., Frackowiak, R. S. J., & Passingham, R. E. (1994). Motor sequence learning: A study with positron emission tomography. *Journal of Neuroscience*, **14**, 3775–3790.
- Jenkins, W. M., Merzenich, M. M., Ochs, M. T., Allard, T., & Guíc-Robles, E. (1990). Functional reorganization of primary somatosensory cortex in adult owl monkeys after behaviorally controlled tactile stimulation. *Journal of Neurophysiology*, **63**, 82–104.
- Kaas, J. H. (1991). Plasticity of sensory and motor maps in adult mammals. *Annual Review of Neuroscience*, **14**, 137–167.
- Karni, A., Meyer, G., Jezzard, P., Adams, M., Turner, R., & Ungerleider, L. (1995). Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature*, **377**, 155–158.
- Karni, A., Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M. M., Turner, R., & Ungerleider, L. G. (1998). The acquisition of skilled motor performance: Fast and slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Science USA*, **95**, 861–868.
- Kawashima, R., Roland, P. E., & O'Sullivan, B. T. (1994). Fields in human motor areas involved in preparation for reaching, actual reaching, and visuomotor learning: A positron emission tomography study. *Journal of Neuroscience*, **14**, 3462–3474.
- Kilgard, M. P., & Merzenich, M. M. (1998). Cortical map reorganization enabled by nucleus basalis activity. *Science*, **279**, 1714–1718.
- Kleim, J. A., Barbay, S., & Nudo, R. J. (1998). Functional reorganization of the rat motor cortex following motor skill learning. *Journal of Neurophysiology*, **80**, 3321–3325.
- Kleim, J. A., Lussnig, E., Schwarz, E. R., Comery, T. A., & Greenough, W. T. (1996). Synaptogenesis and FOS expression in the motor cortex of the adult rat after motor skill learning. *Journal of Neuroscience*, **16**, 4529–4535.
- Merzenich, M. M., Recanzone, G., Jenkins, W. M., Allard, T. T., & Nudo, R. J. (1988). Cortical representational plasticity. In P. Rakic & W. Singer (Eds.), *Neurobiology of neocortex* (pp. 41–67). New York: Wiley.
- Milliken, G. W., Plautz, E. J., Gardner, G. A., Raiszadeh, R., & Nudo, R. J. (1994). Reorganization of movement representations in primary motor cortex of adult squirrel monkeys following distal forelimb restriction. *Society for Neuroscience Abstract*, **20**, 1394.
- Milliken, G. W., Plautz, E. J., & Nudo, R. J. (1995). Recovery of finger movement representation after distal forelimb restriction in adult squirrel monkeys. *Society for Neuroscience Abstract*, **21**, 1902.
- Mitz, A. R., Godschalk, M., & Wise, S. P. (1991). Learning-dependent neuronal activity in the premotor cortex: Activity during the acquisition of conditional motor associations. *Journal of Neuroscience*, **11**, 1855–1872.
- Nudo, R. J., Jenkins, W. M., Merzenich, M. M., Prejean, T., & Grenda, R. (1992). Neurophysiological correlates of hand preference in primary motor cortex of adult squirrel monkeys. *Journal of Neuroscience*, **12**, 2918–47.
- Nudo, R. J., Milliken, G. W., Jenkins, W. M., & Merzenich, M. M. (1996). Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *Journal of Neuroscience*, **16**, 785–807.
- Nudo, R. J., Plautz, E. J., & Milliken, G. W. (1997). Adaptive plasticity in primate motor cortex as a consequence of behavioral experience and neuronal injury. *Seminars in Neuroscience*, **9**, 13–23.
- Pascual-Leone, A., Dang, N., Cohen, L. G., Brasil-Neto, J. P., Cammarota, A., & Hallett, M. (1995). Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *Journal of Neurophysiology*, **74**, 1037–1045.
- Pascual-Leone, A., Grafman, J., & Hallett, M. (1994). Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science*, **263**, 1287–1289.
- Pascual-Leone, A., & Torres, F. (1993). Plasticity of the sensorimotor cortex representation of the reading finger in braille readers. *Brain*, **116**, 39–52.

- Plautz, E. J., Milliken, G. W., & Nudo, R. J. (1995). Differential effects of skill acquisition and motor use on the reorganization of motor representations in area 4 of adult squirrel monkeys. *Society for Neuroscience Abstract*, **21**, 1902.
- Recanzone, G. H., Merzenich, M. M., Jenkins, W. M., Grajski, K. A., & Dinse, H. R. (1992). Topographic reorganization of the hand representation in cortical area 3b of owl monkeys trained in a frequency discrimination task. *Journal of Neurophysiology*, **67**, 1031–1056.
- Recanzone, G. H., Schreiner, C. E., & Merzenich, M. M. (1993). Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *Journal of Neuroscience*, **13**, 87–103.
- Schieber, M. H., & Deuel, R. K. (1997). Primary motor cortex reorganization in a long-term monkey amputee. *Somatosensory and Motor Research*, **14**, 157–167.
- Schieber, M. H., & Hibbard, L. S. (1993). How somatotopic is the motor cortex hand area? *Science*, **261**, 489–92.
- Schlaug, G., Knorr, U., & Seitz, R. (1994). Inter-subject variability of cerebral activations in acquiring a motor skill: A study with positron emission tomography. *Experimental Brain Research*, **98**, 523–534.
- Seitz, R. J., Roland, P. E., Bohm, C., Greitz, T., & Stone-Elander, S. (1990). Motor learning in man: A positron emission tomographic study. *NeuroReport*, **1**, 57–60.
- Singer, W. (1995). Development and plasticity of cortical processing architectures. *Science*, **270**, 758–764.
- Ungerleider, L. G. (1995). Functional brain imaging studies of cortical mechanisms for memory. *Science*, **270**, 769–775.
- Wang, X., Merzenich, M. M., Sameshima, K., & Jenkins, W. M. (1995). Remodelling of hand representation in adult cortex determined by timing of tactile stimulation. *Nature*, **378**, 71–75.
- Waters, R. S., Samulack, D. D., Dykes, R. W., & McKinley, P. A. (1990). Topographic organization of baboon primary motor cortex: Face, hand, forelimb, and shoulder representation. *Somatosensory and Motor Research*, **7**, 485–514.
- Weinberger, N. M. (1995). Dynamic regulation of receptive fields and maps in the adult sensory cortex. *Annual Review of Neuroscience*, **18**, 129–58.
- Weinberger, N. M., & Bakin, J. S. (1998). Learning-induced physiological memory in adult auditory cortex: Receptive field plasticity, model, and mechanisms. *Audiology and Neuro-Otology*, **3**, 145–167.
- Withers, G. S., & Greenough, W. T. (1989). Reach training selectively alters dendritic branching of subpopulations of layer II–III pyramidal neurons in rat motor–somatosensory forelimb cortex. *Neuropsychologia*, **27**, 61–69.
- Xerri, C., Coq, J. O., Merzenich, M. M., & Jenkins, W. M. (1996). Experience-induced plasticity of cutaneous maps in the primary somatosensory cortex of adult monkeys and rats. *Journal of Physiology (Paris)*, **90**, 277–287.
- Zar, J. H. (1984). *Biostatistical analysis*. Englewood Cliffs, NJ: Prentice-Hall.
- Zhuang, P., Dang, N., Warzeri, A., Gerloff, C., Cohen, L. G., & Hallett, M. (1998). Implicit and explicit learning in an auditory serial reaction time task. *Acta Neurologica Scandinavica*, **97**, 131–137.
- Zohary, E., Celebriani, S., Britten, K. H., & Newsome, W. T. (1994). Neuronal plasticity that underlies improvement in perceptual performance. *Science*, **263**, 1289–1292.