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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

Nancy N. Byl, PhD, PT; Michael M. Merzenich, PhD; and William M. Jenkins, PhD

Article abstract—In this study we tested a neuroplasticity/learning origins hypothesis for repetitive strain injuries (RSIs), including occupationally induced focal dystonia. Repetitive movements produced in a specific form and in an appropriate behavioral context cause a degradation of the sensory feedback information controlling fine motor movements, resulting in the "learned" genesis of RSIs. Two adult New World owl monkeys were trained at a behavioral task that required them to maintain an attended grasp on a hand grip that repetitively and rapidly (20 msec) opened and closed over short distances. The monkeys completed 300 behavioral trials per day (1,100 to 3,000 movement events) with an accuracy of 80 to 90%. A movement control disorder was recorded in both monkeys. Training was continued until the performance accuracy dropped to below 50%. We subsequently conducted an electrophysiologic mapping study of the representations of the hand within the primary somatosensory (SI) cortical zone. The hand representation in the true primary somatosensory cortical field, SI area 3b, was found to be markedly degraded in these monkeys, as characterized by (1) a dedifferentiation of cortical representations of the skin of the hand manifested by receptive fields that were 10 to 20 times larger than normal, (2) the emergence of many receptive fields that covered the entire glabrous surface of individual digits or that extended across the surfaces of two or more digits, (3) a breakdown of the normally sharply segregated area 3b representations of volar glabrous and dorsal hairy skin of the hand, and (4) a breakdown of the local shifted-overlap receptive field topography of area 3b, with many digital receptive fields overlapping the fields of neurons sampled in cortical penetrations up to more than four times farther apart than normal. Thus, rapid, repetitive, highly stereotypic movements applied in a learning context can actively degrade cortical representations of sensory information guiding fine motor hand movements. This cortical plasticity/learning-based dedifferentiation of sensory feedback information from the hand contributes to the genesis of occupationally derived repetitive strain injuries, including focal dystonia of the hand. Successful treatment of patients with RSI will plausibly require learning-based restoration of differentiated representations of sensory feedback information from the hand.

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Repetitive strain injuries (RSIs), or repetitive motion injuries (RMIs), are defined as chronic soft-tissue inflammations accompanied by scarring, pain, fatigue, muscle spasm, postural imbalance, nerve entrapments, and movement dysfunction that result from excessive and repetitive end-range motions, force, and stretching.[1-4] Secondary swelling narrows important structures and creates nerve-root impingements or nerve entrapments such as carpal tunnel, cubital tunnel, or thoracic outlet syndromes. Reflex sympathetic dystrophy and occupational hand cramps (focal dystonia of the hand) can be later complications.[5-14] RSIs usually occur in workers who perform repetitive motor movements under conditions of high cognitive drive, e.g., computer programmers, data-entry clerks, keyboard users, meat cutters, musicians, assembly-line workers, and truck drivers.[1]

Movement repetition is the major risk factor in 84% of cases.[1,4]

Nearly all medical specialists studying and treating these conditions accept the premise that repetitive movements lead to peripheral biomechanical microtrauma expressed as chronic inflammation and tissue anoxia.[2,4,7,11,12,15,16] The symptoms initially abate when the affected individual rests the involved extremity or modifies the manner of performance, e.g., angling the wrist differently, using less force, or transferring movement more proximally.[4] Interventions such as systemic medications, local injections, stress reduction, joint protection with splinting, strengthening, restoration of flexibility, modification of the workstation, redesign of instruments and tools, warming up before work, taking frequent breaks, or surgery may temporarily relieve the

symptoms, but the symptoms resurface when the patient returns to work.[4,17-21]

The repetitive nature of an attended work task simulates conditions that are highly effective for remodeling primary somatosensory (SI) cortical areas in learning/neuroplasticity studies conducted in adult monkeys.[22,23] Those studies show that the S1 cortical field representing cutaneous and kinesthetic inputs from the forelimb, as well as motor cortical fields,[24,25] are remodeled by repetitive sensory inputs and movements generated in a behavioral conditioning task. Under carefully controlled input conditions using "natural" forms of inputs, remodeling results in progressively more refined and more differentiated cortical representations of skin, muscle, joint afferent fibers, and motor movements.[22-24,26-33] This occurs, for example, when inputs delivered in a behavioral training context consistently move across the skin or engage it with significant trial-by-trial locational variation.[33-35] In the competitive cortical processes that underly changes induced in learning, the dynamic network machinery interprets each not-precisely-simultaneous input source as separate and different.[32,33] At the same time, the normal operations of this cortical plasticity machinery can also lead to degraded representations in the more artificial input circumstances in which afferent activities are (1) highly repetitive, (2) highly spatially stereotyped, (3) synchronously engaging normally differentiated sensory feedback inputs, and (4) cognitively important, e.g., delivered in an attended behavior.

In humans, the requisite condition of nearly simultaneous costimulation could hypothetically arise, for example, by adoption of hand positions like the stereotyped grasp of a pen during writing or holding a golf club, both of which generate simultaneous activations of skin and muscle afferent fibers that are temporally exaggerated by contact events. It could arise from fast, attended movements, sensory stimulation, or rapid alternating movements (e.g., production of a trill by finger movements on a musical instrument) that nearly simultaneously engage (within the 10- to 100-msec-long integration time of the cortical plasticity machinery) normally differentiated afferent inputs and movements.[22,26,32,35-37] These neuroplastic changes only occur in models of cortical learning for inputs that are repetitive and behaviorally attended. Repetitive, passive inputs generate little enduring change.[22,26-31,38,39] To a highly variable extent, work-induced changes that are normally offset by other more varied daily behaviors can be expected to delay the predominance of repetition-induced functional changes.

We report an experiment representing an assay of the possible relationship between these dramatic behaviorally induced cortical plasticity effects and RSI–focal dystonia symptomatology. Using a behavioral model of repetitive hand opening and closing with two adult owl monkeys, we asked: (1) In what specific ways are cortical "maps" of the skin degraded by highly stereotypical and repetitive move-
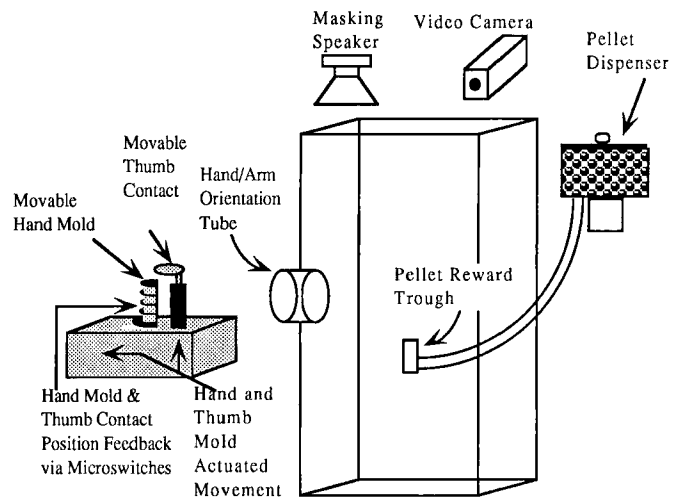

Figure 1. Sensory motor training apparatus designed to engage an adult monkey in a repetitive exercise that introduced limited-scale (1.5 mm for the thumb and 6 mm for the four long fingers), very rapid openings and closings of the hand.

ment behaviors? (2) When clinical signs of RSIs and a degradation of movement control for the hand develop, what is the status of the cortical representations of sensory inputs from the hand?

Methods. *Subjects.* Two adult female owl monkeys (OM nos. 175 and 281) served as the subjects. Although their exact age was unknown, they were judged to be young adults by their weights and their full complement of adult dentition.[40] Both animals were neurologically intact and had no previous experimental use. Both monkeys had a strong left-hand preference on the pretraining food retrieval task and the training task. The study protocol was approved by the Animal Research Committee before initiating the study.

Behavioral training. Both monkeys engaged in a behavioral training task 5 to 6 days per week over 12 (no. 175) and 25 weeks (no. 281), respectively. Training was conducted in a cage mounted in a sound-isolated test chamber. A video system external to the cage monitored the monkeys' behavior. A short cylinder mounted on the cage front guided the monkeys' reach to a hand grip molded to precisely fit each monkey's vertically oriented hand. A pellet feeder was attached to a side wall of the cage. The monkeys were placed on a controlled diet and deprived of food for 20 to 22 hr before training. Nutritionally complete, whole-grain, banana-flavored pellets of 45 mg (Bio-serve, Frenchtown, NJ) served as behavioral rewards. Monkeys received water ad libitum, as well as food supplements (vitamins and fruit) immediately after each daily training period.

The monkeys were first trained to reach out of the cage through a cylindrical opening. They were then trained to reach out and grasp a hand grip formed from two half cylinders (figure 1). A thin, oval thumb plate was mounted on top of this grip. Contact detectors were mounted on the thumb plate and in each finger groove. When the monkey achieved a stereotyped hand grip that activated all of the contact detectors on the hand grip, stimulation was initiated. The goal of the behavioral training was to create a

paradigm of rapid opening and closing of the fingers that would approximate a simultaneous movement. Driven by a spring-loaded solenoid, the outer half of the hand grip moved in a horizontal direction to open and then close by the action of the spring. The thumb pad was mounted on a second spring-loaded solenoid, which opened and closed the thumb. The excursion of the fingers was 6.4 mm; the thumb plate moved 1.5 mm. The passive finger and thumb openings occurred within 16 msec. Closure required approximately 50 msec.

This behavioral apparatus was controlled by a LabVIEW virtual instruments program. In each trial, the fingers and the thumb opened one to nine times, with the number of movement cycles determined randomly. The monkey initiated the task by placing the fingers and thumb on the hand grip to activate all contact detectors. Illumination of a light-emitting device signaled to the monkey that this response condition had been achieved. The monkey had to maintain all fingers and the thumb in contact with the handpiece during the entire opening and closing cycle. The feeder delivered a pellet each time the monkey successfully performed this task. Both monkeys performed approximately 300 trials per day and experienced 1,100 to 3,000 attended, stereotyped openings and closings of the hand in each 1- to 2-hr-long daily training period. The monkeys trained at 80 to 90% accuracy.

Motor performance. Focal dystonia of the hand is a difficult diagnosis to make in humans as well as in animals. Thus, the criteria used to judge the onset of simulated occupational hand cramps included the following: (1) an inability to perform the training task at 80 to 90% accuracy, (2) marked difficulty opening or closing the hand on the handpiece, (3) a decrease in the rate of performance (average number of task repetitions per fixed time interval), and (4) a measurable decline in performance on the efficiency of food retrieval using a parallel evaluative paradigm. All of these conditions were met in both monkeys.

Training sessions were videotaped to assure appropriate task performance. Training continued after the initial onset of the movement disorder until each monkey deteriorated in task performance to achieve a success level of less than 50% for a period of at least 2 weeks. Signs of tremors, pain, and difficulty opening and closing the hand were subjectively documented from the daily observation of the videotapes. In addition, 5-min videotape segments were randomly observed throughout the training period, thereby documenting the speed of performance (task repetitions per minute) throughout the training period.

Although focal dystonia of the hand is very specific to a target task, there is commonly some carryover of motor dysfunction to other similar tasks. To assess general motor hand dysfunction, an ordinal scale was created to measure the efficiency of food retrieval. Monkeys were evaluated at baseline and at the end of the behavioral training period just before mapping. Each monkey completed two trials of the following retrieval task sequence: (1) retrieval of nine pieces of fruit from a tray with small wells, one at a time, with the items varying in size from 2 to 16 mm, and (2) retrieval of nine food items (small rectangular piece of apple) presented through a cylindrical tube with the targets presented to the left, right, top, and bottom of the cylinder opening, and one cylindrical piece presented in a

vertical orientation in the middle of the feeding tube. This series of retrieval tasks was videotaped for later scoring.

The videotapes were viewed in slow motion and the hand retrieval movements were graded by four independent observers trained in hand movement kinesiology. All reviewers were blinded to the monkeys' identity and status of training. Each retrieval was graded on the following scale: 5 = successful retrieval of the item on the first attempt, with smooth and efficient movement; 4 = successful retrieval of the item on the first attempt, with movement not smooth or efficient; 3 = successful retrieval of the item on the second attempt, with smooth and efficient movement; 2 = successful retrieval of the item on the second attempt, with movement not smooth or efficient; 1 = successful retrieval of the item on the third attempt; 0 = successful retrieval of the item in four or five attempts; and −1 = could not retrieve the presented item.

Each rater was asked to note the type of prehension that the monkey used, but this was not scored on these retrieval tasks. The average efficiency scale was determined for the tray retrieval activities and the feeding tube activities. Nine items were scored for each of these two tasks.

A pilot test was carried out with this instrument before initiating the behavioral study in the trained monkeys. Four different monkeys were filmed during the administration of the food retrieval tasks. Four different examiners independently rated each monkey. Using the intraclass correlation coefficient, the agreement was 0.97 for the items on the tray feeding and 0.86 for the items retrieved from the feeding tube. Although interrater agreement was 0.98 for the type of grasp used, this information was not included in the final instrument scoring. Intrarater reliability was 0.91 for both of the task series.

Surgery and electrophysiology. The goal of this electrophysiologic study was to define the neuronal responses and the cortical representations ("maps") of the hand surfaces, i.e., cutaneous receptors, in the trained cerebral hemispheres of these two experimental monkeys. The hemisphere contralateral to the trained hand was studied. Anesthesia was induced with a 1.5% halothane/75% N_2O/25% O_2 gas mixture to allow for placement of a venous catheter. The monkeys were subsequently anesthetized with sodium pentobarbital given to effect (initial dose, 28 mg/kg IV) and maintained at a surgical level of anesthesia by intravenous supplementation. Heart rate and blood pressure were monitored. A lactated Ringer's solution with 5% dextrose was continuously infused intravenously (6 ml/hr) and adjusted as indicated by cardiovascular system monitoring and skin integrity to maintain body hydration. Core temperature was maintained at 38 °C. The bladder was emptied at regular intervals. Animals were maintained areflexic throughout these long experiments. Atropine sulfate (0.1 mg every 12 hr) and penicillin G (30,000 U every 24 hr) were administered at the onset of these electrophysiologic experiments, and penicillin G was supplemented every 12 hr thereafter to maintain an acceptable blood level of this prophylactic antibiotic. The entire experiment was performed using sterile surgical procedures to maintain preparation viability for the relatively long recording times required to generate these elaborate maps.

The cortical mapping procedures employed in this study have been described in several earlier reports from this

laboratory.[22,26,28-31,41-45] Surgically anesthetized monkeys were mounted in a stereotactic apparatus. A wide craniotomy exposed the anterior parietal cortex centered on S1 cortical area 3b. The dura was carefully resected and a well for sterile, high-viscosity silicon oil was constructed. A Sony CCD camera mounted on a WILD operating microscope was used to record a computer image of the cortical surface vasculature (40×) and the dorsal and glabrous surfaces of the trained hand.

Parylene-coated tungsten microelectrodes with 1- to 3-mOhm impedances (at 1 kHz) were used for recording. All microelectrode penetrations were parallel to one another and were introduced roughly perpendicular to the cortical surface. Each insertion site was marked on the image of the cortical surface by reference to vascular details. Data were collected at a depth of 700 to 800 microns below the cortical surface (corresponding to deep cortical layer 3 in area 3b). Unit and multiple single-unit recordings were amplified, bandpass filtered, and displayed by the use of conventional methods.

Using a fine-tipped, opaque glass probe, the receptive fields were defined for each cortical penetration. The skin stimulus criterion of "just-visible skin indentation" was used for all receptive-field definitions. Reference studies reported that just-visible indentations are in the range of 250 to 500 microns, the middle of the dynamic range of large-fiber cutaneous mechanoreceptor afferent fibers.[46-49]

After the penetration site was marked on the cortex, the receptive field(s) for each sampled neuron(s) was carefully drawn to scale on the computer hand image by using a mouse cursor and cortical mapping software.[50] When receptive fields overlapped onto different functional hand surfaces, cortical representational boundaries were drawn to reflect proportional overlaps.

For OM no. 175, area 3b was mapped for 15 hr and the monkey was recovered. In OM no. 281, areas 3b and 3a were mapped for 72 hr. Normal maps of the SI cortex (3b) are well documented and available for reference, serving as controls for this study.[41]

Data analysis. MAP[50] software was used to reconstruct cortical representations and to measure cutaneous receptive fields. Experimental receptive field sizes were compared with the mean receptive field sizes derived using the same methods, as reported in the literature. Student's t test was used to determine the significance of differences from the trained animals and controls ($p < 0.025$ to control for multiple testing). Student's t test was also used to determine the significance of the scale changes on the two sections of the food retrieval task for each animal ($p < 0.025$). The decline in speed of performance was analyzed using the Page test for trends from the beginning to the end of the training ($p < 0.05$).

Results. *Behavioral histories.* After a few weeks of training at the grasping task, both monkeys were able to successfully and reliably maintain hand contact during digit and thumb openings and closings, performing the task at 80 to 90% accuracy. After 5 weeks of training for the first monkey and 8 weeks of training for the second monkey, both began to have difficulty removing their hand from the handpiece. After several days of poor behavioral performance, both monkeys were observed to adjust to and then overcome this problem by markedly reducing the force of their grip on the handpiece. Several weeks later,
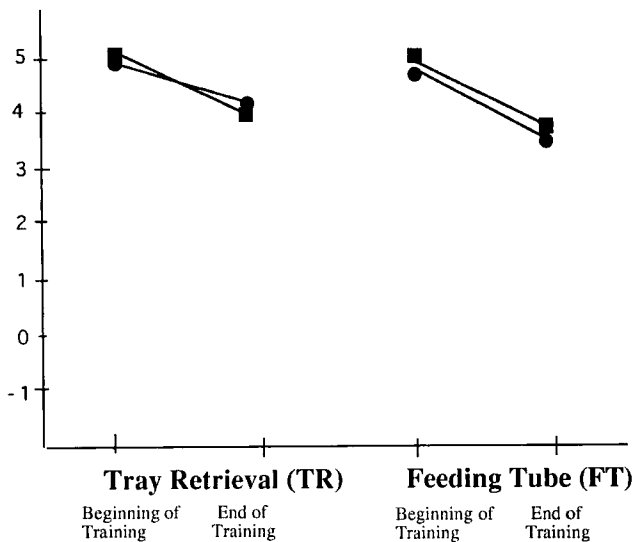
one monkey (OM no. 175) developed an apparent tendinitis that was marked by the monkey voluntarily performing only a limited number of trials in succession, and then attending to its hand between trials by licking or sucking the thumb. After a period of rest for 8 days, these signs of tendinitis disappeared and the monkey no longer attended excessively to its hand. However, in this completely voluntary behavior, this monkey was subsequently reluctant to undergo intensive training, reducing the number of trials to approximately half the number completed in earlier daily training sessions. Four weeks later, the monkey began to have consistent difficulty making contact on the handpiece with fingers 2 and 4. To enable continued training, the contact detectors for fingers 2 and 4 had to be turned off. Four weeks later, the monkey was failing more than 50% of the trials, meeting the target training goal for scheduling the electrophysiologic mapping studies.

After relatively early temporary evidence of motor difficulties relieved by the relaxation of grip force, the second monkey (OM no. 281) performed a full complement of daily trials over a subsequent 3-month period. After that time, no signs of tendinitis were observed, but this monkey also began to have difficulty making complete contact of the digits with the handpiece. To continue the training, the contact detector for either digit 2 or 4 had to be turned off. Despite this adjustment, the monkey failed at more than 50% of the trials, and was therefore scheduled for electrophysiologic mapping.

Both monkeys exhibited changes in hand retrieval patterns. After about 4 months of training, OM no. 175 no longer employed its initially strongly dominant left hand in small object or food retrieval tasks, reflecting a shift in hand dominance to the right hand. On the retest, only 20% of the items were retrieved with the left hand and consequently rescored. Figure 2 summarizes the changes in food retrieval efficiency for both monkeys. The monkey was very efficient on the baseline food retrieval task, scoring a mean ± SD of 5 ± 0 on the food tray tasks and 4.95 ± 0.23 on the feeding tube tasks. Based on 72 trial measurements scored at each test, the mean efficiency scale decreased significantly ($p < 0.0001$) on both tasks, with the mean ± SD decreasing to 4.25 ± 1.46 and 4.06 ± 1.39 on the food tray and feeding tube tasks, respectively. OM no. 281 showed significant ($p < 0.0001$) deterioration in performance efficiency on both the tray feeding task (a decrease from a mean ± SD of 5.0 ± 0 to 4.46 ± 0.74) and the feeding tube task (decreased from 4.88 ± 0.33 to 3.97 ± 0.73). The monkeys either did not use an efficient pattern of retrieval or did not pick up the food on the first attempt.

Both monkeys also showed a significant, decreasing monotonic trend ($p < 0.0001$) in their speed of task performance. Thus, in addition to a decline in accuracy of task performance, they also showed a significant decrease in their performance rates (figure 3).

Degradation of hand representations in cortical area 3b. The representations of the surfaces of the hands in cortical area 3b were substantially altered in these two adult monkeys by this repetitive hand-use working experience. Changes were substantially more severe in the monkey that had developed clear signs of an enduring "tendinitis." The dedifferentiation of neuronal responses and the

Figure 4. Histogram of the differences in the average size of the digital receptive fields for the trained monkeys compared with the reference control monkeys. *When all receptive fields of fingers which included the whole hand are included in this average, the mean ± SD size of the receptive fields for owl monkey (OM) 281 is 150.4 ± 237.5 mm^2.
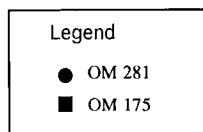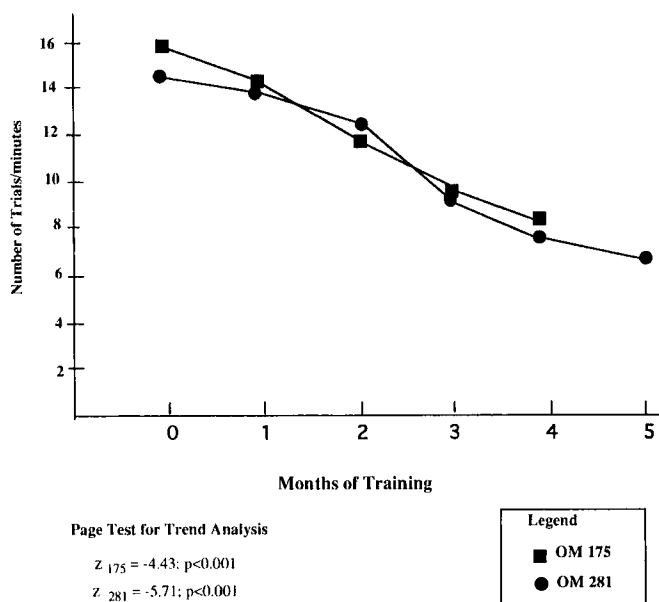
Figure 2. Line graph summarizing the decline in performance efficiency on the food retrieval tasks. OM = owl monkey.

degradation of cortical topographies were marked by a number of changes in cortical area 3b.

Cortical representations of the skin were dedifferentiated. The selectivity of cortical neuronal responses is indicated by the size of the cutaneous receptive fields, i.e., by the skin surface areas that provide effective inputs to sampled neurons. In normal owl monkeys, digital receptive

field areas generally range from 1 to 15 mm^2, with 90% of receptive field areas falling between 2 and 9 mm^2.[51] The average digital receptive fields in this species is 8.0 ± 3.0 (SD) mm^2.[51] Receptive fields for the two trained monkeys were significantly larger than normal (figure 4). For OM no. 175, the mean size of digital receptive fields was 78.0 ± 22.5 (SD) mm^2, about 10 times larger than normal. In OM no. 281, the mean size of digital receptive fields was 150.4 ± 237.5 (SD) mm^2, more than 20 times the normal size. When nine of the receptive fields covering most of the glabrous and dorsal hand surface were deleted from the sample, the average receptive field size was 94.7 ± 103.8 (SD) mm^2, still more than 10 times the normal size. A significant number of sampled receptive fields covered the entire glabrous surfaces of a digit (figure 5, D and E, open circles), which is rarely recorded normally. There was poor differentiation between the locations of different, sampled receptive fields on the proximal, middle, and distal aspects of the digits (figure 6). In both monkeys, a large number of sampled neurons had receptive fields that extended across more than two glabrous segments of one finger. Such entire-digit receptive fields are not commonly recorded in this cortical area in "naive" monkeys.[41-43,52]

It might be noted that the definition of the boundary between cortical areas 3b and 3a was relatively clearly defined in OM no. 175 on functional grounds. Receptive fields on the glabrous skin that progressed topographically to the extreme fingertip zone under the fingernails were recorded in a number of samples along the area 3b side of this border; neurons studied in the next-most-rostral penetrations proceeding rostrally responded only to noncutaneous afferent inputs, with responses that were typical for
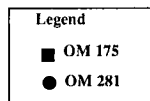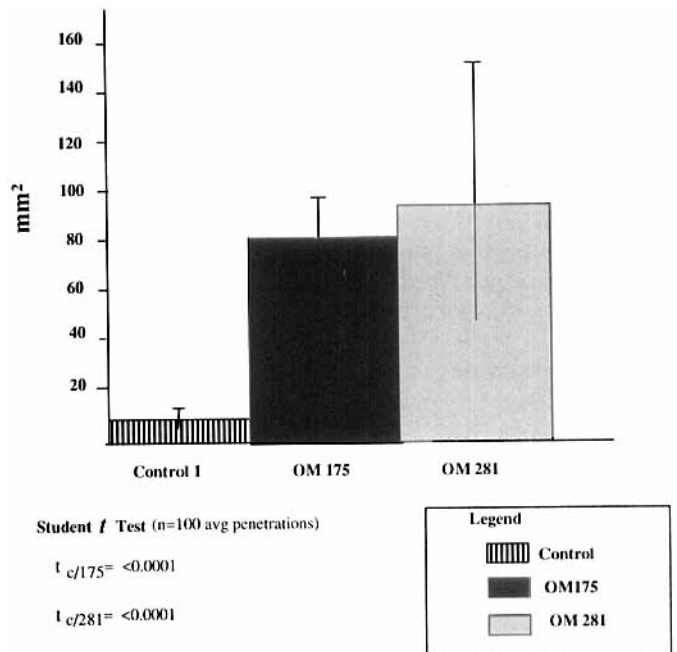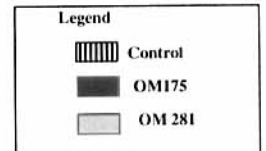

Figure 3. Line graph of the monotonic decline in the speed of performance on the target task, i.e., repetitive passive opening and closing of the hand. OM = owl monkey.
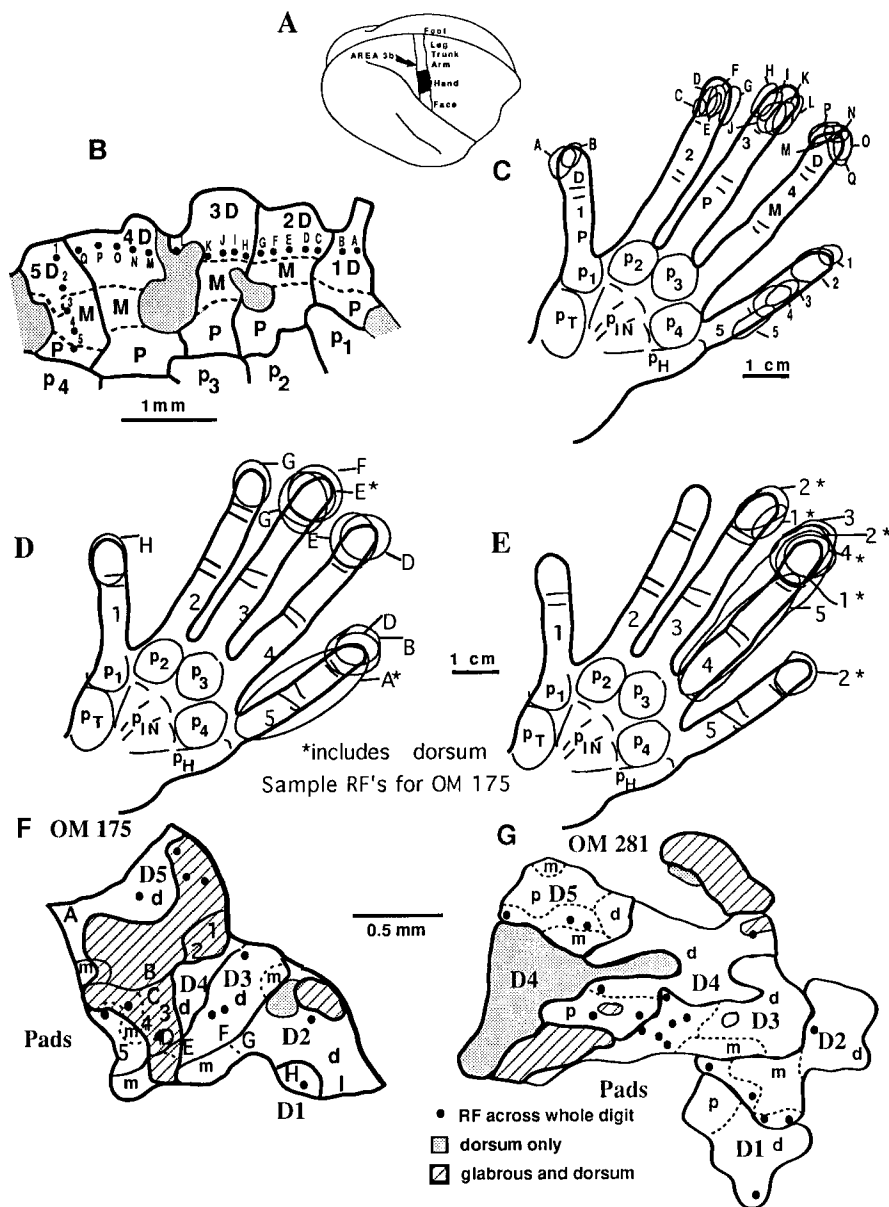
Figure 5. (A) Hand zone in cortical area 3b in the anterior parietal cortex. (B) Typical normal receptive fields (RFs) on the hand, representing the hand surfaces topographically by a shifted-overlap representational schema. Penetration sites at which receptive fields were recorded are illustrated (1–5, A–Q) in the normal "map" of the hand in (C). (C) Territories over which neurons were driven with receptive fields on different hand surfaces are outlined (1–5, A–B). Area 3b hand zones representing dorsal hand surfaces are shaded. (D–G) Territories over which the neurons were driven with receptive fields on the different hand surfaces, and topographically representational schema of area 3b in the two experimental monkeys. In the monkeys, receptive fields commonly extended from the dorsal to the glabrous skin (hatched). Receptive fields at many sites covered the entire glabrous or glabrous plus dorsal surfaces of at least one finger. Neither of these features is ordinarily recorded in normal monkeys. OM = owl monkey; D = distral; M = middle; P = proximal segments of the fingers; 1–5 = digits; P_I-P_4, P_H, P_{IN}, and P_T = pads of the palm.

area 3a. This functional boundary was not as clear in OM no. 281, in which the most rostrally recorded neuronal samples that were sensitive to cutaneous stimuli responded to stimulation of broad surfaces of multiple fingers, with only a handful of receptive fields limited to a single-digit tip segment recorded anywhere in area 3b. The cutaneous afferent-responding region defined in area 3b in this monkey was very small.[41] The cortical hand representational areas for the glabrous surface of the digits for OM nos. 175 and 281 were 1.3 mm^2 and 1.98 mm^2, respectively, compared with the range of 3.2 to 5.1 mm^2 for nine normal owl monkeys.[41] However, in the absence of clear topographic mapping criteria, the absolute location of the 3b/3a border was not functionally defined, and it is possible that the zone defined functionally as cortical area 3b may have included a small number of samples that were actually derived from area 3a. However, because the great majority of large, abnormal receptive fields in this case were recorded in what was unequivocally cortical area 3b,

this possible limited contamination of these data does not alter any of the main conclusions of this study.

Breakdown in the normally separated representations of different hand digits. Digital representational zones in cortical area 3b are normally sharply segregated from one another.[37,41,53] Receptive fields innervating the glabrous skin in normal adult owl monkeys are almost always limited to the skin surfaces of one or two segments of a single finger. By contrast, in these two monkeys, multiple-digit receptive fields were recorded at many penetration sites. In OM no. 175, neurons sampled in 51% of the penetrations in area 3b had multiple-component receptive fields with subfields on more than one digit. In OM no. 281, neurons sampled in 25% of the penetrations in area 3b representing the glabrous surfaces of the fingers had multiple-digit receptive fields, recorded principally in the representational zones of digits 2, 3, and 4 (see figure 6). This breakdown in the separate representations of the digits in this normally strictly topographically organized cor-

OM 175

AREA 3a

D5

Pads

D4

D3

D2

D1

OM 281

AREA 3a

D5

D4

D3

D2

Pads

D1

- ▨ Dorsum
- ▦ Pads on digit
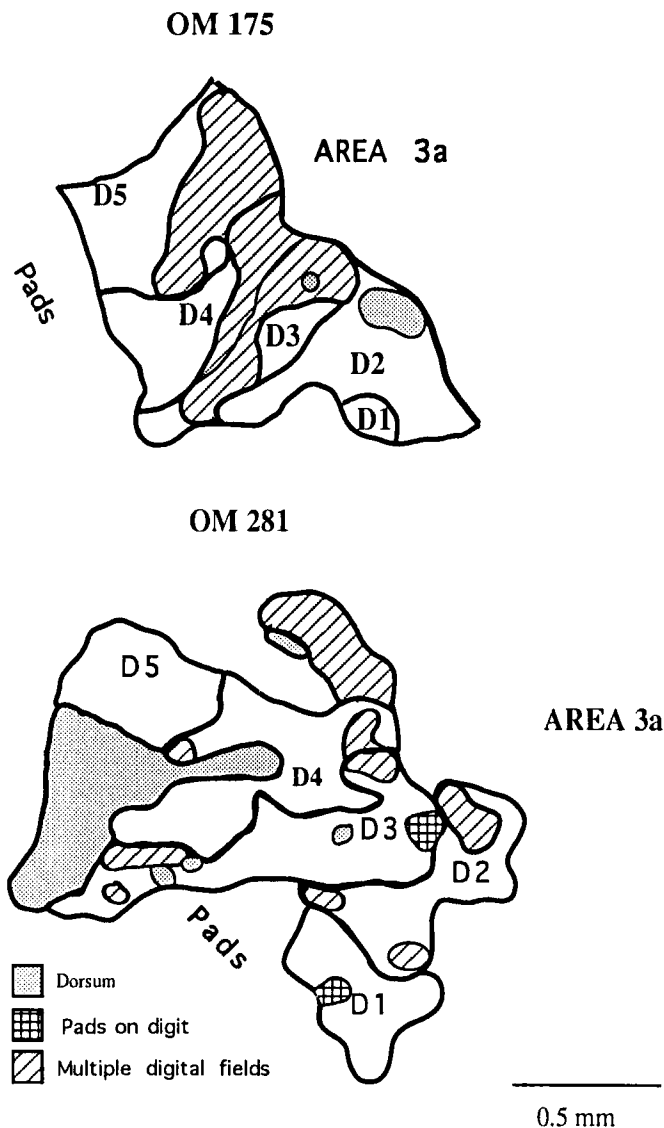- ▨ Multiple digital fields

0.5 mm

Figure 6. Cortical zones for the two monkeys over which all neurons had multiple receptive field components on more than one digit (hatched), receptive fields that had multiple digits and palmar components (crosshatched), or receptive fields restricted to a single digit (open areas). OM = owl monkey.

tical area is illustrated in another way in figures 7 and 8. There, all of the receptive fields were drawn from each individual "digit zone" in the area 3b hand map. Although the typical cortical representation of a digit is normally very specific (see figure 5, B and C), in these trained monkeys, the representation of each digit also had strong inputs from other adjacent digits. The large entire-digit and multiple-digit receptive fields in these cortical area 3b samples did not appear to be pacinian-driven afferent fibers—that is, they were not sensitive to transmitted vibration as effected by tapping wrist tendons, sharply tapping a bony process, or tapping the table on which the hand rested.

Breakdown of the normally segregated representations of volar glabrous and dorsal hairy skin. In normal adult monkeys, receptive fields of neurons in cortical area 3b relatively rarely extend from the glabrous onto the hairy

skin.[52,53] By contrast, such two-surface receptive fields were frequently recorded in these two monkeys. In OM no. 281, neurons in 60 penetrations had dorsal receptive fields; of these, 53% extended onto glabrous skin surfaces. In OM no. 175, 19 penetrations had a dorsal receptive field; 90% of them extended far onto glabrous skin surfaces.

Breakdown of local representational topography and a cortical "hypercolumn rule." The degradation of these normally highly differentiated skin representations was also shown by the sequences of change in selective cortical neuronal responses recorded across the area 3b maps in these cases. In the normal adult cortex, area 3b receptive fields shifted continuously as successive samples were derived across these cortical maps. As a rule, receptive fields normally no longer overlap when samples are derived more than about 400 to 500 microns apart.[23,54] This overlap distance is roughly constant across area 3b in a normal adult New World squirrel or owl monkey.[23,54] That means that stimulation of any given spot on the skin evokes responses in cortical neurons over an approximately constant, roughly half-millimeter-diameter area 3b zone; any part of any given receptive field is represented by cortical neurons over a relatively constant, roughly one-millimeter-diameter cortical zone.

These measures of the selectivity of responses in the horizontal dimension of the cortex are radically altered in these trained monkeys. In both monkeys, stimulation of a skin site on the tips of digits 2, 3, or 4 resulted in the excitation of neurons across a cortical region that was up to about 2 mm across. A detailed analysis of the extents of overlap of paired receptive fields relative to the distances between the unit response sampling cortical penetrations in OM no. 175 is illustrated in figure 9. The distances between sampled neuron pairs ranged from approximately 100 to 2,000 microns. Seventy percent of receptive fields over that distance overlapped completely with at least one other receptive field, and there was no clear indication of a falloff in the percentage of overlapping receptive fields as a function of distance, as occurs in normal monkeys. Thus, the cortical zone representing any given point on the skin of the hand, or representing any given hypothetical cutaneous receptive field, was several times greater than normal in this monkey.

Segmental organization of the representation of the digits. With the irregular and often slow shifts in cortical receptive field location and overlap as a function of distance across the cortical map, the detailed topography of these maps was difficult to reconstruct. The normal, orderly shifted receptive field sequences recorded in these monkeys[41,53] was replaced by more complex sequences of multiple-digit and large, single-digit receptive fields. Although this topography was grossly abnormal, a general digit 1 to digit 5 mediolateral progression and a general digit tip to proximal digit segment rostrocaudal progression was recorded in both of these monkeys.

Discussion. This study was designed to test the hypothesis that at least some of the phenomology of repetitive strain injuries, particularly those associated with movement disorders, might arise because of an experience-induced degradation of sensory feedback in the cerebral cortex. After several months

Multiple RF's
including Digit 1

Multiple RF's
including Digit 2

Multiple RF's
including Digit 3

Multiple RF's
including Digit 4

Multiple RF's
including Digit 5

10 mm

Note:
*9 cortical penetrations
had receptive fields over
the entire glabrous or
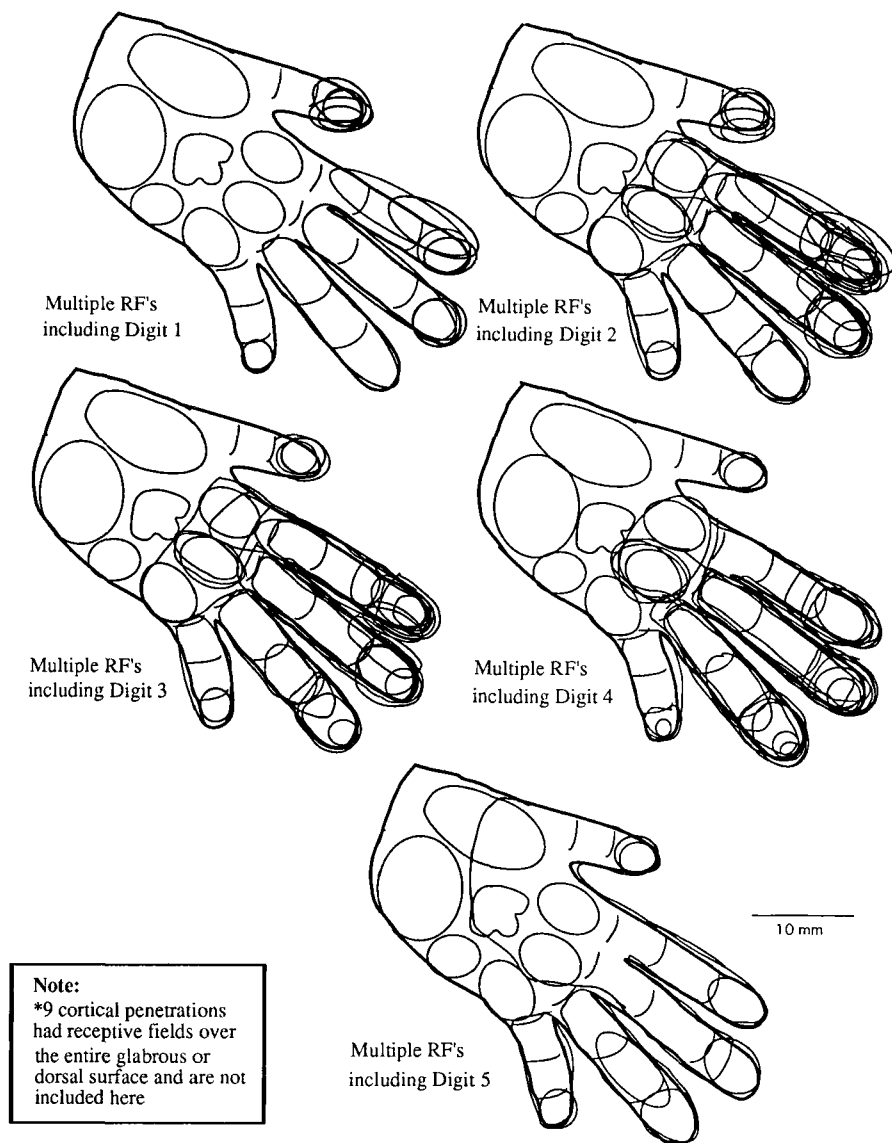dorsal surface and are not
included here

Figure 7. All digital receptive fields (RFs) from owl monkey (OM) 281 recorded in area 3b zones sorted by individual digit, including all of the associated receptive fields overlapping onto adjacent digits. Compare to figure 2, C and D. These reconstructions illustrate the lack of independent representation of the five hand digits in area 3b in this monkey.

of daily exercise at a sensory-guided, repetitive hand task involving opening and closing of the five hand digits while they were held in contact with a hand grip, there was a substantial dedifferentiation of the representation of the surfaces of the hand in the most representationally differentiated and most orderly cortical representational field in the somatosensory domain of adult primates, cortical area 3b. There was a breakdown of the normally sharply independent representations of fingers in this cortical field. Receptive fields representing the hand digits in this field were, on average, 10 to 20 times larger than normal. Multiple-digit receptive fields were more common than the normal single-digit receptive fields, and there was a significant breakdown of the normally segregated representations of the glabrous volar and the hairy dorsal hand surfaces. Stimulation of any small skin locations engaged neurons over an area many times larger than normal.

Implications for underlying cortical plasticity processes. The changes recorded in these monkeys are consistent with a general conclusion drawn from ear-

lier cortical plasticity experiments that induced changes are coincident input based, i.e., arising from synaptic change mechanisms that are Hebb-like in origin.[55] In this current experiment, the glabrous and dorsal hairy skin of multiple fingers was nearly simultaneously engaged by sharp 6.4-mm and 1.6-mm movements of the digits on the hand grip and thumb plate. As an apparent consequence of nearly simultaneous skin afferent engagement over wide hand sectors, neurons at many area 3b sites developed responses to multiple-digit and glabrous/dorsal input combinations that are not normally recorded in this field. In addition, receptive field size changes were several times greater than even those generated by a complete local block of inhibitory inputs in area 3b in macaque monkeys,[56] indicating that progressive plasticity of long-range intracortical (or other) connections contributed to them.

This study provides another example of experience-based alteration of cortical "hypercolumn" dimensions.[22,26-32,42-45,57,58] In these monkeys, stimulation of a given skin site evoked neuronal re-

Multiple RF's
including Digit 1

Multiple RF's
including Digit 2

Multiple RF's
including Digit 3

Multiple RF's
including Digit 4

10 mm

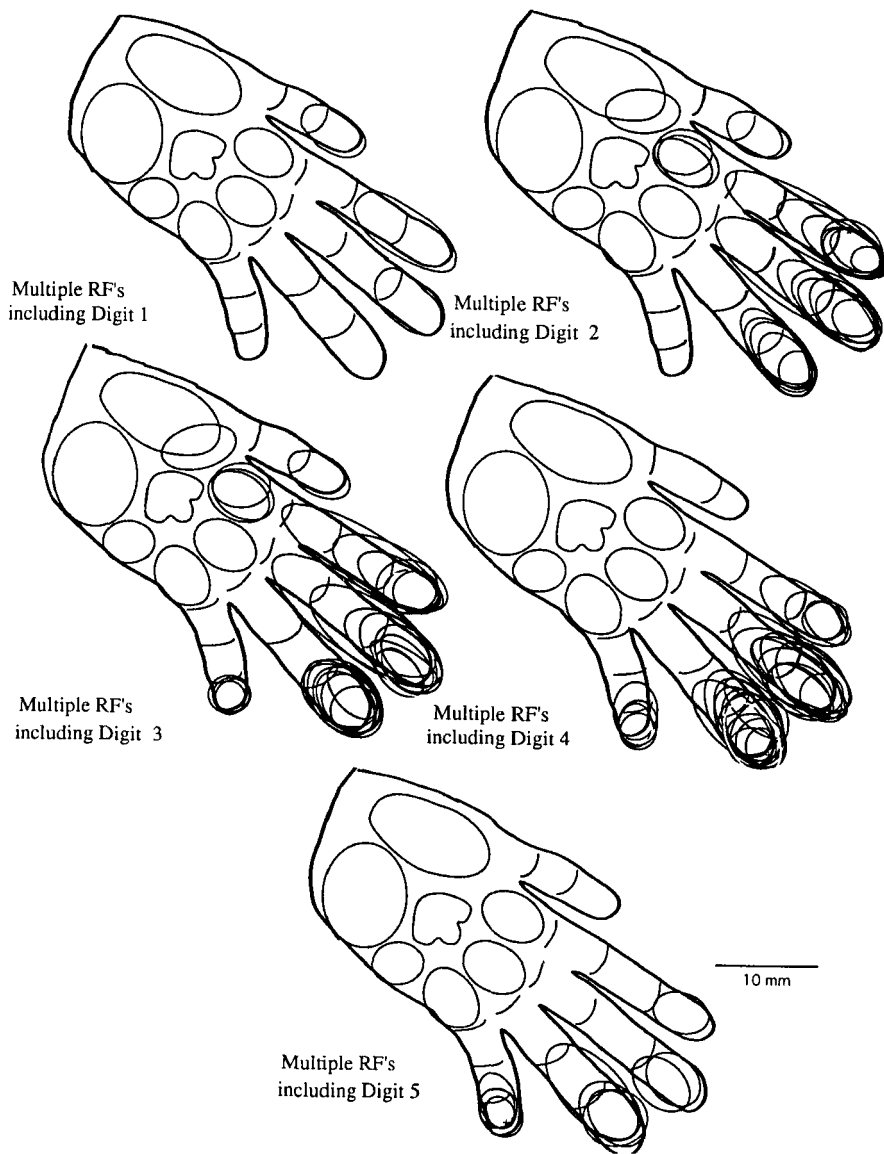Multiple RF's
including Digit 5

Figure 8. All digital receptive fields in owl monkey (OM) 175 recorded in area 3b zones sorted by individual digit, including the associated receptive fields overlapping onto adjacent digits.

sponses over a much larger than normal cortical area. At the same time, another prediction of the dynamic maintenance of the "hypercolumn rule"[22,23,26,27,44,45,57,58] may partially apply. As receptive fields became enlarged, the cortical territories representing the overall skin surface should contract proportionally. Although that contraction was far from proportional, the overall territory of the cortical representation of individual digits appeared to be smaller than normal in both of these two monkeys.

How could these changes in area 3b contribute to the genesis of a work-induced movement disorder? Cortical area 3b (the true SI cortex) has only relatively modest direct projections to area 4 (the "primary" motor cortex) in this species.[59-62] This direct area 3b-to-4 projection may be even more sparse or absent in other primates, including humans.[61-64] At the same time, area 3b has topographic, strongly anatomically expressed connections to five principal anterior and ventral parietal cortical fields that, in turn, have major, topographically ordered projections to area 4 in the owl monkey (areas 3a, 1, 2, 5, and
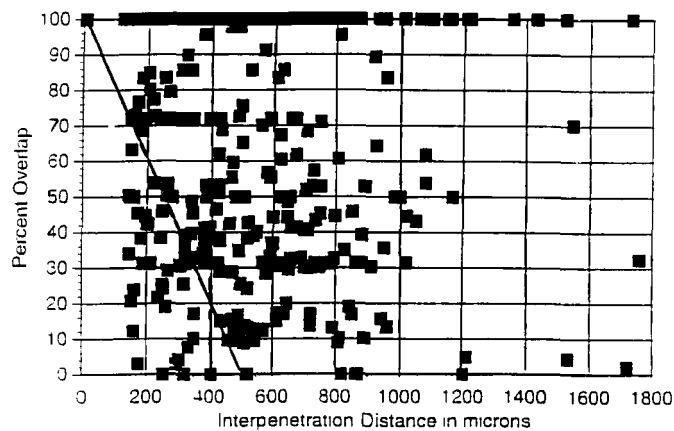

Figure 9. Percent overlaps for pairs of glabrous receptive fields as a function of distance separating sampled neuronal pairs, for all combinations of all receptive fields in owl monkey (OM) 175. The straight line represents the normal receptive field overlap versus cortical distance function recorded in these monkeys.

SII).[60,62,63,65-68] Moreover, area 3b has strong, orderly projections to at least three other functional regions that provide strong direct projections into area 4: (1) the supplementary motor cortical areas;[59,64] (2) a strip of cortex in premotor area 6 that borders area 4;[59] and (3) the subcortical putamen.[69] With its central position as the true SI cortical field, the substantial changes in the area 3b representation of the hand, consequent to the behavioral training, would also be expected to substantially influence cortical area 4.[22,51,70-72]

Recent studies of Pavlides et al.[73] affirm the critical importance of SI cortex inputs for motor skill learning. Tactually guided motor-skill learning in macaque monkeys requires an intact SI cortex. Hikosaka et al.[74] found digital manipulation and grasping of small objects to be grossly degraded by temporary anesthesia of restricted sectors of SI cortical area 2. We recently recorded similar effects after the induction of microlesions in area 3b in monkeys trained at a similar small-object retrieval task.[23] In that experiment, cortical microlesions produced by bipolar coagulation of surface vessels followed the derivation of detailed hand representation maps in trained owl monkeys. Those microlesions were designed to selectively destroy *only* the area 3b representations of the fingertips that each monkey used to palpate and manipulate pellets in a learned behavior. The performance of these monkeys at pellet retrieval was dramatically degraded by these microlesions, and monkeys behaved as if these digital surfaces were insensate. They commonly adopted a behavioral strategy in which they peeked into their partially opened hand on each behavioral trial to determine whether they had successfully grasped a pellet (they usually had not) before they brought the hand up to the mouth. Monkeys recovered from this striking functional deficit only after several more weeks of behavioral training. That retraining resulted in newly emergent plastic changes in digit tip representations, now most strongly expressed in cortical area 3a and/or 1 (C. Xerri, M. Merzenich, and W. Jenkins, unpublished observations).

Implications for the origins of RSIs. The repetitive, stereotyped, behaviorally attended, rapidly alternating inputs in this study generated major changes in even the most topographically ordered of the cortical maps of feedback inputs from the hand. When work-induced sensory inputs are in the appropriate form and are generated in the right behavioral context, as they are in these monkeys, they should profoundly degrade cortical representational specificity, largely destroying the independent representation of digits and reducing the information-bearing capacity of the cortex by expanding the dimensions or overlaps of input-specific cortical columns.

What are the important conditions for work activities that must be achieved to generate this representational degradation? *First, input activity patterns must be rigidly stereotyped.* Even small trial-by-trial variations in engaged skin surfaces or movements can result in refinement, not degradation, of sensory input representations.[22,23] *Second, inputs must be repetitive.* Learning-induced changes are generated progressively in monkeys, with the formation of well-learned movement representations strengthened continuously over many successive days and weeks of practice. *Third, repetitive motion events must nearly simultaneously engage normally differentiated sensory inputs.* In learning, the effectivenesses of nearly simultaneous inputs are integrated by the operation of Hebb-like synaptic plasticity mechanisms. Even a relatively small statistically consistent separation of input events will result in the segregation—and not the integration—of inputs delivered into the cortex on a heavy behavioral schedule.[32,33,35,75] *Fourth, inputs must be attended in the work behavior.* Behaviors performed automatically (i.e., with low or no attention) drive weak or no significant plasticity changes in the cortex.[33-35]

Both monkeys in this study changed the force of their grip after several-day-long periods of experiencing difficulty with grip release. This may have signaled an episodic period of pain, discomfort, or loss of voluntary grasp control. The monkey who exhibited the greater area 3b representational changes was also the monkey that later appeared to develop an enduring tendinitis. Inputs from pain afferent fibers could conceivably directly alter receptive field dimensions in this cortical area, as with cutaneous receptive fields in the anatomically parallel dorsal horn system.[76,77] In contradistinction to spinal experiments, blocking of small afferent fibers has been found to generate enlargement of cortical receptive fields,[78,79] an effect that is at variance with a positive pain-mediated spinal receptive field effect.

Pain is a powerful behavioral reinforcer. The presence of pain could be a direct contributor to, or an enabler of, the cortical plasticity changes recorded in these monkeys. Based on this interpretation, the dedifferentiating-induced cortical changes might be magnified by the true etiology of RSI symptoms: mechanically induced irritation or inflammation in the hand or limb. Patients with early signs of pain associated with repetitive motion injury may be at risk for movement disorders if the pain amplifies cortical plasticity dedifferentiation effects. On the other hand, pain is not a necessary element for dramatic neuroplasticity effects. In other monkey studies, large-scale representational changes are recorded in the absence of pain.[22,23,26,32]

Whatever the role of nociceptive inputs, the striking degradation of these cortical maps must have neurobehavioral consequences. These two monkeys demonstrated significant motor behavioral consequences. However, it is difficult to confirm that the motor dysfunction was specifically a focal dystonia of the hand. One monkey became reluctant to use the trained hand that had earlier been dominant for small-object and food retrieval behaviors. Both monkeys became highly significantly clumsier at a variety of object retrieval behaviors, and both deterio-

rated markedly in their performance on the repetitive hand opening and closing task. There was no simple way of assessing the tactile sensibilities or the haptic capacities of these monkeys, but they would certainly be expected to be altered in the face of these major changes in feedback information guiding refined movement control.[80] In addition, there was no way to ask the monkeys to describe why they were unable to completely grasp the handpiece or whether they experienced any abnormal, involuntary, uncontrollable movements when they initiated the grasp.

The behavioral paradigm used in this study should also have resulted in the degradation of the cortical areas representing muscle afferent, joint afferent, and other proprioceptive feedback from the hand and forearm, e.g., motor cortical areas, SI cortical areas 3a and 2, and other parietal cortical areas including areas 5 and SII. Changes in those cortical zones will be the subject of later reports in this RSI/RMI/focal dystonia model experimental series.

In many patients with RSI, the resolution of painful tendinitis does not result in recovery of other symptoms. A nonpainful focal dystonia can then emerge in the patient, and be sustained for long periods in the absence of frank pain. The dystonia itself likely reflects, and possibly directly arises from, the degradation in cortical representations that have been induced by the "learned" repetitive inputs, possibly historically enabled or amplified by an earlier period of painful movement. Again, cortical plasticity experiments[22,24,26,27,32-35] report *major* cortical representational changes in behaviors that *never* appeared to be painful to the monkey. Thus, while pain may contribute to the amplification of plasticity effects and the genesis of work-induced movement disorders, we emphasize that it is probably not necessary for their progressive development.

An alternative RSI origins hypothesis. An alternative RSI origins scenario is supported by this (and other) cortical plasticity experiments: (1) repetitive inputs alter brain representations of cutaneous and deep afferent feedback signals, thereby altering corticofugal distributions and strengths of inputs to sympathetic and pain centers, contributing to the emergence of an inflammatory response expressed in the arm; (2) the degradation of sensory feedback quality accounts for the uncontrolled cocontractions that commonly mark the movement dysfunction reported by patients with RSI (occupational hand cramps). Human imaging studies by Flor et al.[81] provide recent evidence supporting this view. The extent of plastic reorganization in arm amputees is directly correlated with the degree of pain referred to an amputated limb, suggesting that the occurrence of "phantom limb" pain may be directly related to the topographic distributions of cutaneous inputs in a reorganizing SI or primary motor cortex.

Related observations in patients with RSI. In two recent studies reported by Byl et al.,[80,82] patients with repetitive injuries defined as tendinitis or focal hand dystonia had discriminative sensory processing problems. Those with tendinitis had significant problems with kinesthesia; those with focal hand dystonia had significant problems with graphesthesia and stereognosis. These skills require cortical processing and could reflect some degradation in SI cortical fields. Neither patient group had difficulty with a simple tactile localization task, even when stimuli were restricted to the specific digits that were most affected by the dystonia, even though some patients reported simultaneous sensations occurring widely across a finger, on the back of the hand, etc. This finding of normal localization of tactile stimuli may be at variance with the conclusions of this current monkey experiment, may represent the lack of sensitivity of the task, or may support the recent suggestion that stimulus location may be signaled by neuronal population coding that can actually be sharpened by deriving population information from wider filter bandwidth (larger receptive field) sources.[83,84]

Study limitations. There are several important limitations of the present study that are the subject of further current investigations. First, insofar as the behavior, the opening and closing of the hand was passive, albeit with a requirement for maintenance of an active hand grip in an attended behavior. In most repetitive injury conditions, the repetitive movement involves active, voluntary movements. Second, the monkey adjusted to an early, emergent movement dysfunction by simply changing the force of hand gripping. Both of these behavioral limitations are circumvented in a current experimental series, which requires active opening and closing against a known force. Third, the definition of focal dystonia of the hand in monkeys was based on direct observation. Objective cortical sensory testing cannot be done, nor can the monkey easily provide us with descriptions of fatigue, awkwardness, and subtle involuntary muscle contractions. To document this state more objectively, electromyographic studies might be able to document uncontrollable cocontraction of agonists and antagonists during a target task.

Possible implications for the remediation of RSI. If forebrain representational degradation contributes to the triggering of limb inflammation, pain, fatigue, and awkward movements, then restoring normally ordered representations of feedback inputs from the tactile and proprioreceptive receptors of the limb may block the progression of these conditions and may reverse them to reestablish a "safe zone" of movement operation. This redifferentiation of sensory feedback information and movement could be hypothetically accomplished by a series of repetitive, cognitively demanding sensory receptive, haptic, and movement exercises designed to progressively reestablish cortical map order and differentiation. Even if the true origin of the pain and inflammation marking RSI is biomechanical, the repetitive inputs that generate it must also be degrading representations of movements and feedback signals from skin, mus-

cles, and joints. The emergence of ultimately pain-free dystonia in these patients could hypothetically reflect the individual extent to which that is the case. The many hundreds to tens of thousands of hours of repetitive inputs that lead to RSI probably generate what are essentially *learned* changes in forebrain representational zones. These must be reversed by a period of learning-based exercises, designed to redifferentiate and reorder degraded representations of movements and afferent feedback sources.[85]

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**A primate genesis model of focal dystonia and repetitive strain injury: I.
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