proposed (22) that PCP passes energy from its chlorophylls to those of the membrane-bound LHC. Although the data (22) do not exclude direct energy transfer to the core of photosystem 2, the similar appearance of the PCP trimer and that of the intrinsic chlorophyll-carotenoid protein suggests that PCP and LHC could coexist in a stacked configuration. With this proposed geometry, highly efficient Förster energy transfer from PCP to LHC can be expected, because the tetrapyrrole rings of their chlorophylls would be approximately coplanar.

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Neural Substrates for the Effects of Rehabilitative Training on Motor Recovery After Ischemic Infarct

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Substantial functional reorganization takes place in the motor cortex of adult primates after a focal ischemic infarct, as might occur in stroke. A subtotal lesion confined to a small portion of the representation of one hand was previously shown to result in a further loss of hand territory in the adjacent, undamaged cortex of adult squirrel monkeys. In the present study, retraining of skilled hand use after similar infarcts resulted in prevention of the loss of hand territory adjacent to the infarct. In some instances, the hand representations expanded into regions formerly occupied by representations of the elbow and shoulder. Functional reorganization in the undamaged motor cortex was accompanied by behavioral recovery of skilled hand function. These results suggest that, after local damage to the motor cortex, rehabilitative training can shape subsequent reorganization in the adjacent intact cortex, and that the undamaged motor cortex may play an important role in motor recovery.

The motor cortex is thought to be important in the initiation of voluntary motor actions, especially those associated with fine manipulative abilities. Thus, a stroke or other injury to the motor cortex results in weakness and paralysis in the contralateral musculature and disruption of skilled limb use (1). However, a gradual return of some motor abilities often occurs in the weeks and months after injury (2). At least in humans, complete recovery of function in distal musculature, including independent control of digits, is rare (3).

Neurophysiological and neuroanatomical bases have been sought to account for functional motor recovery after cortical injury. It is assumed that other parts of the motor system must "take over" the func-

tion of the damaged cortex, but the precise neural mechanisms by which lost functions are regained are poorly understood (*4*). Early studies suggested that lost cortical functions are assumed by the cortical tissue adjacent to the zone of injury (*5*). Others have suggested that cortical motor areas in the same or opposite hemisphere, or subcortical structures, may play a role in recovery (*6*). Despite more than a century of study, direct experimental evidence for any one of these hypotheses is scarce.

In the 1950s, Glees and Cole used surface stimulation techniques to show that, after a lesion of the thumb representation area in the motor cortex, the thumb representation reappeared in a zone surrounding the infarct (*5*). Although maps of motor topography were not presented, this study is one of the earliest direct demonstrations of a representational change within the cerebral cortex after a focal injury. Few comparable studies have been done since the introduction of contemporary intracortical microstimulation (ICMS) techniques (*7*).

To examine lesion-induced plasticity in the primary motor cortex (also called M1 or area 4) of primates in more detail, we have used ICMS techniques to derive detailed maps of the hand representation in adult squirrel monkeys before and after focal ischemic infarcts. ICMS procedures are now widely used for mapping the functional topography of the motor cortex (*8–10*). In a previous study with ICMS techniques, we examined spontaneous reorganization after infarct (*10*) and showed that movements represented in the infarcted zone did not reappear in the cortical sector surrounding the infarct. Instead, hand movement representations adjacent to the infarct that were spared from direct injury underwent a further loss of cortical territory.

Because we did not use any specific motor training procedures in our initial study, it is possible that such losses in the representational area of the hand are the direct result of diminished use of the affected hand (*8, 10*). Conversely, it is possible that rehabilitative training after the injury could result in enhancement of representational plasticity and of functional motor recovery. To explore this latter possibility, we conducted the following experiments. First, four monkeys underwent a training procedure that required skilled use of the hand to retrieve food pellets from small wells (*11*). Two days after behavioral criteria were attained, we applied ICMS mapping techniques (*12*). From these physiological studies, motor maps were drawn that outlined cortical efferent zones, the intracortical stimulation of which evoked specific movement subsets (*13*). Infarcts were then induced by bipolar electrocoagulation of a small vascular bed over an electrophysiologically identified portion of the motor cortex hand area (*14*). Within 5 days after the infarct, monkeys began an intensive behavioral retraining procedure identical to that used before the infarct, which was continued until preinfarct performance levels were attained. In three of the four monkeys, the ICMS mapping procedure was then repeated (*15*).

The infarct initially resulted in a marked deficit in the ability to retrieve food pellets, especially from the smallest wells. In the first several days after the infarct, movements were slow and monkeys had difficulty placing fingers into the smallest target wells. Manual skill, as measured by the total number of finger flexions per pellet retrieval, was markedly reduced and was more variable from trial to trial. More specifically, the number of flexions per retrieval from the smallest well on the final day of preinfarct training was 1.8 ± 0.92, 2.7 ± 0.82, 2.0 ± 0.82, and 7.4 ± 4.0 (means ± SD) for monkeys 1 through 4, respectively. During the initial period of rehabilitative training after the infarct, these values increased to 7.5 ± 7.8, 7.8 ± 7.3, 50.3 ± 59.9, and 17.4 ± 17.4, respectively (*16*). However, skill improved and variance decreased rapidly during the subsequent several days of rehabilitative training (Fig. 1). In contrast, hand function was normal in the largest wells throughout the postinfarct period. Training continued until preinjury performance levels were achieved with the smallest well (3 to 4 weeks). On the final day of rehabilitative training, the number of flexions per retrieval was 1.5 ± 0.85, 1.6 ± 0.70, 2.9 ± 2.6, and 8.2 ± 4.1, respectively.

In two monkeys, a period of rapid improvement in manual skill was followed by a relapse to skill levels apparent immediately after the infarct. This period of relapse was then followed by a second period of rapid improvement and stabilization within the normal range (Fig. 1) (*17*). Although the importance of the relapse is not clear, this observation suggests that secondary degenerative changes or diaschisis can occur in the adjacent, undamaged motor cortex (or other motor structures interconnected with the infarcted tissue) for at least several days after focal infarct.

Comparison of ICMS maps of movement representations before and after the infarct revealed substantial rearrangement of representations surrounding the lesion. Spared hand representations appeared to invade adjacent regions formerly occupied by representations of the elbow and shoul-

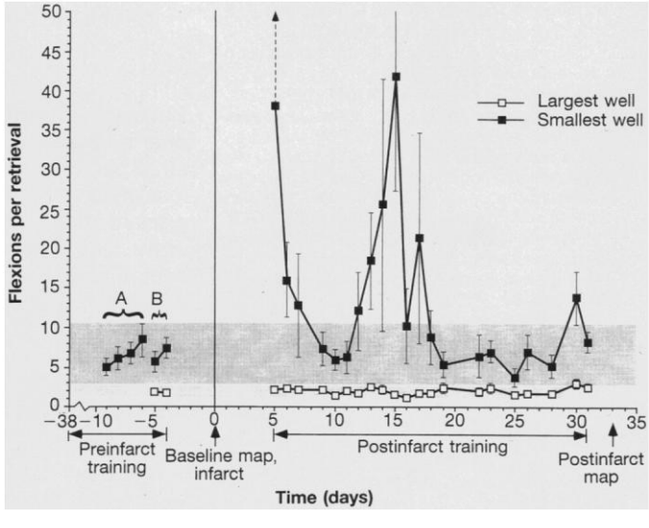

Fig. 1. Effects of ischemic infarct on manual skill. Four squirrel monkeys underwent daily training on a task requiring skilled use of the hand, especially the fingers. Normal retrieval of food pellets from the smallest well required the insertion of one or two fingers, as well as specific movement sequences and combinations (*8*). Normal retrieval from the largest well was accomplished by insertion and simultaneous flexion of all fingers. Data points represent the mean (±SEM) number of flexions per retrieval for each day, with optimal performance being one flexion per retrieval. The shaded regions indicate the 95% confidence intervals for preinfarct performance (dark shading, smallest well; light shading, largest well). Bracket A represents the final phase of the titration procedure, during which trials were conducted only on the smallest well, and bracket B represents the preinfarct probe phase (2 days), during which random probe trials were conducted on each of five wells. During postinfarct training, random probe trials were conducted on each day. The dashed arrow above the data point on postinfarct day 5 indicates that no retrievals were made from the smallest well on that day. Although the number of flexions per retrieval is plotted here as a daily measure of manual skill, final criterion performance (both pre- and postinfarct) was based on the total number of pellets retrieved per day from the smallest well (*11*).

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der. This invasion occurred over distances of up to 3 mm. Quantitative assessment of representational area showed a net expansion of the hand area in the zone immediately surrounding the infarct in two retrained monkeys and no change in the third (20.5, 14.6, and −0.3%, respectively; mean, 11.6%) (Fig. 2). In one animal, expansion resulted in a hand representation that was larger than the entire representation before the infarct, including the infarct zone. When the hand representation was subdivided into digit and wrist-forearm representations, the digit area increased in two retrained monkeys and decreased in a third (14.9, 6.5, and −32.7%, respectively), although the mean change was small (3.8%), which was similar to changes seen in control animals. However, the wrist-forearm area increased in each of the three retrained monkeys (58.5, 22.6, and 80.0%, respectively), with a mean increase of 53.7%.

Comparison of the changes in motor representations among the control, rehabilitation, and previously described spontaneous recovery (*10*) groups revealed several statistically significant differences (*18*). The percentage change in each of the three movement categories differed significantly among the three groups (hand, $F = 7.94$, $P = 0.013$; digit, $F = 8.15$, $P = 0.012$; and wrist-forearm, $F = 6.53$, $P = 0.021$). Post hoc analysis verified our previous data showing that the hand and digit areas decreased significantly in the spontaneous recovery group when compared with controls (*10*). The present results reveal that changes in the areal extent of movement representations did not differ significantly between rehabilitation and control groups (hand, mean difference = 15.6%, $P = 0.251$; digit, mean difference = 1.5%, $P = 0.926$; wrist-forearm, mean difference = 60.7%, $P = 0.026$) (Fig. 3). However, because the wrist-forearm area increased in each of the retrained monkeys, a larger sample may reveal a systematic increase after postinfarct rehabilitative training, raising the possibility that retrained monkeys learned new behavioral strategies to accomplish the pellet retrieval task after the infarct (*19*).

Because representational maps in spontaneously recovered animals showed significant differences from those in control animals (*10*), our present data suggest that rehabilitative training resulted in prevention of the loss of spared hand area in the adjacent, intact cortex. Post hoc comparison of the two infarct groups revealed statistically significant differences in reorganization of hand representations (mean difference = 47.9%, $P = 0.005$). When hand representations were subdivided into digit and wrist-forearm representations, the loss in digit area seen in spontaneously recovered monkeys was not evident in monkeys that underwent rehabilitative training (mean difference = 53.6%, $P = 0.010$). In addition, the wrist-forearm area increased significantly in monkeys undergoing rehabilitation as compared with those that recovered spontaneously (mean difference = 77.7%, $P = 0.008$) (*20*). Because spontaneously recovered monkeys did not wear jackets, it is possible that the differences between the two groups are simply due to the increased use of the impaired hand in the jacketed monkeys and not specifically to rehabilitative training. However, we regard this possibility as unlikely on the basis of preliminary data from two additional monkeys that wore jackets restricting the nonimpaired hand but did not receive rehabilitative training after the infarct. In these monkeys, digit area decreased by an average of 42.3% (−29.2 and −55.5%, respectively) and wrist-forearm area decreased by an average of 14.5% (−17.2 and −11.8%, respectively), which was similar to results from spontaneously recovered monkeys.

Studies conducted over the past several years have revealed that representational maps in the sensorimotor cortex of adult primates are alterable as a function both of the integrity of their sensory inputs and of experience (*8*, *21*). In addition, recent studies in humans with a variety of techniques have suggested that motor cortical areas are modifiable as a result of central or peripheral pathology or of motor skill learning (*22*). Together with the present results, these studies suggest that motor experience after injury to the motor cortex plays a major role in the subsequent phys-

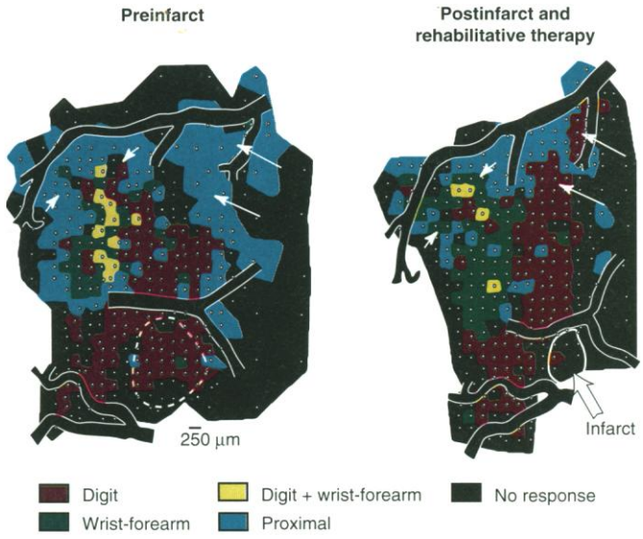

Fig. 2. Reorganization of hand representations in the primary motor cortex before infarct (left) and after a focal ischemic infarct and rehabilitative training (right). At each microelectrode penetration site (small white circles), ICMS techniques were used to define movements evoked by near-threshold electrical stimulation (<30 μA). In this animal, the infarct destroyed 21.6% of digit and 4.1% of wrist-forearm representation. After rehabilitative training, the spared digit representational area increased by 14.9% and the spared wrist-forearm representational area increased by 58.5%. The dashed circle in the preinfarct map encompasses cortical territory targeted for ischemic infarct. The large white arrow in the postinfarct map indicates the infarcted region. The reduction in size of the infarcted zone is attributable to tissue necrosis during the rehabilitation period. Long thin arrows point to adjacent, undamaged cortex in which digit representations (red) appear to have invaded regions formerly occupied by representations of the elbow and shoulder (blue). Short thin arrows point to wrist-forearm representations (green) that appear to have invaded digit, elbow, and shoulder representations.

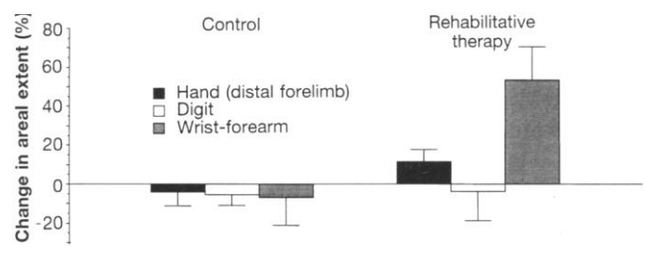

Fig. 3. Changes in the areal extent of hand representations in the control group ($n = 4$) and rehabilitative training group ($n = 3$). The changes differ substantially from those observed in spontaneously recovered monkeys in a previous infarct study [mean values of −36.4, −57.4, and −24.0% in hand, digit, and wrist-forearm representational areas, respectively (*10*)]. Movement categories are exclusive; that is, dual-response representations, such as digit plus wrist-forearm (*8*), are not included. Data are means ± SEM.

iological reorganization that inevitably occurs in the adjacent, intact tissue. It is possible that functional reorganization in the motor cortex underlies the improvement in motor function seen in human stroke patients undergoing similar rehabilitative therapy. In chronic stroke patients, Taub *et al.* (*23*) showed that constraint of the upper extremity of the unaffected limb for 14 days results in long-term improvement of motor function in the impaired limb. Our previous study of reorganization in the motor cortex after spontaneous recovery from a focal infarct implies that, in the absence of postinjury rehabilitative therapy, the surrounding tissue undergoes a further territorial loss in the functional representation of the affected body part (*10*). Whether this loss is due to "learned nonuse" (*23*) or to disruption of local (intrinsic) cortical circuitry remains to be determined. The present study suggests that rehabilitative therapy prevents further losses of hand area in the adjacent, intact tissue, and may direct the intact tissue to "take over" the damaged function. It is not clear whether such reorganization is due to physical growth of new axonal processes or to modulation of existing synapses. It is important to address these questions in future studies, because knowledge of the neural substrates that underlie the recovery of motor function may lead to new therapeutic approaches to treatment for stroke that are guided by the rules governing functional plasticity in the cerebral cortex.

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11. Eight adult male squirrel monkeys (*Saimiri boliviensis* spp.) were used in the present study. Four monkeys were randomly assigned to a training group and four to a control group (no infarct, no training). The control group served to assess the relative stability of ICMS-derived motor maps in the absence of any manipulation other than the mapping procedure itself. After determination of hand preference (*8*), a jacket was placed on each monkey with a sleeve that extended the length of the nonpreferred forelimb, covering the hand. The monkey wore the jacket for the remainder of the experiment (both pre- and postinfarct periods), except during surgical procedures. In normal monkeys, this jacket does not markedly impair pellet retrieval. Training was conducted with a rectangular Plexiglas board containing five food wells of different diameters, ranging from 9.5 to 25 mm. Two 30-min sessions were conducted per day. The target well size was gradually titrated to produce progressively more retrievals from the smaller wells, until all training trials were conducted on the smallest well. Preinfarct training continued until 600 pellets were retrieved from the smallest well on each of two consecutive days (criterion performance). On the two subsequent preinfarct days, sessions consisted of 25 probe trials followed by training trials. During probe trials, a single 45-mg banana-flavored food pellet was placed randomly into one of the five wells, and the animal was allowed to retrieve it. During training trials, a single food pellet was placed into the target well. Sessions consisting of a combination of probe and training trials were continued during the postinfarct period to track recovery.
12. Under sterile conditions and halothane–nitrous oxide anesthesia, the primary motor cortex was exposed. A small cylinder was fitted over the opening and filled with warm, sterile silicone oil. Halothane was withdrawn, ketamine-acepromazine was administered, and vital signs were monitored throughout the remainder of the experiment. A glass micropipette filled with 3.5 M NaCl served as the microelectrode. It was introduced on a fine grid pattern, sited with reference to the surface vasculature (interpenetration distances of ~250 μm), and then advanced perpendicular to the cortical surface to a depth of 1700 to 1800 μm (layer V). Movement fields were defined by determining movements evoked by ICMS with near-threshold current levels (maximum current, 30 μA). For further details of these procedures and a discussion of the possible sources of variation in ICMS-defined motor maps, see (*8, 9*).
13. A computer algorithm was used to delineate functional boundaries of movement representations unambiguously. The hand representation, as defined here, comprises cortical regions in which ICMS evoked distal forelimb movements at near-threshold current levels. These distal forelimb movements include finger, thumb, wrist, and forearm (supination and pronation) movements but exclude elbow and shoulder movements. The mosaical representations of movements in the primary motor cortex have been noted in several mapping studies in primates, including humans (*8, 22*) [J. N. Sanes, J. P. Donoghue, V. Thangaraj, R. R. Edelman, S. Warach, *Science* **268**, 1775 (1995)]. After completion of these experiments, each animal was injected with a lethal dose of pentobarbital (100 mg per kilogram of body mass) and perfused for histological examination.
14. Monkeys were anesthetized with halothane–nitrous oxide. A small functional zone was identified in the motor cortex contralateral to the preferred hand with the use of previously derived representational maps. This zone comprised 26.7 ± 8.5% (mean ± SD) of the total hand area and contained a larger proportion of digit than wrist-forearm representational area (31.5 and 16.6%, respectively). Blood vessels supplying this cortical zone were permanently occluded where they entered the cortical surface with the use of microforceps connected to a bipolar electrocoagulator. This technique consistently produced focal, columnar infarcts through all six layers of the cerebral neocortex that were of predictable size and did not extend into the underlying white matter (*10*). These procedures were approved by the University of Texas Institutional Animal Care and Use Committee.
15. The fourth monkey did not survive the postinfarct mapping session.
16. Because two monkeys made no retrievals from the smallest well on the first postinfarct training days, the number of flexions per retrieval was derived from the first 10 retrievals, spanning 1 to 3 days.
17. In a third monkey, relapse was not apparent because manual skill was much more variable. In a fourth monkey, no attempts were made until postinfarct day 13, after which manual skill gradually improved.
18. Statistical analyses were performed with a factorial analysis of variance design to examine variation in the percentage change in each movement area among the three groups ($P \leq 0.05$). Post hoc multiple comparisons (Bonferroni-Dunn) were then performed to determine which pairwise comparisons contributed to significant main effects. Pairwise comparisons were not significant unless the P-value was <0.0167. In both pre- and postinfarct maps, only representations in the cortex outside of the infarct zone were considered for analysis.
19. Alternatively, the differential changes observed in digit and wrist-forearm areas may be related to the location of the infarcts. In each instance, the infarct destroyed a greater proportion of digit, as opposed to wrist-forearm, area.
20. Infarct size and location were similar in the two groups (size: $t = 0.37$, $P = 0.73$). However, it is possible that changes in monkeys undergoing rehabilitation were attributable to the relatively short interval between pre- and postinfarct mapping procedures (4 to 5 weeks). Preliminary results from two additional monkeys indicate that the loss in the spared hand representational area after an infarct and spontaneous recovery are greater at 1 month than at 3 to 4 months [R. J. Nudo, B. M. Wise, F. SiFuentes, *Soc. Neurosci. Abstr.* **21**, 517 (1995)]. Thus, if time after infarct had been matched, the difference between the spontaneous recovery group and the rehabilitation group would probably have been greater.
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