INVITED REVIEW

ABSTRACT: Based upon neurophysiologic, neuroanatomic, and neuroimaging studies conducted over the past two decades, the cerebral cortex can now be viewed as functionally and structurally dynamic. More specifically, the functional topography of the motor cortex (commonly called the motor homunculus or motor map), can be modified by a variety of experimental manipulations, including peripheral or central injury, electrical stimulation, pharmacologic treatment, and behavioral experience. The specific types of behavioral experiences that induce long-term plasticity in motor maps appear to be limited to those that entail the development of new motor skills. Moreover, recent evidence demonstrates that functional alterations in motor cortex organization are accompanied by changes in dendritic and synaptic structure, as well as alterations in the regulation of cortical neurotransmitter systems. These findings have strong clinical relevance as it has recently been shown that after injury to the motor cortex, as might occur in stroke, post-injury behavioral experience may play an adaptive role in modifying the functional organization of the remaining, intact cortical tissue.
 Muscle Nerve **24:** 1000–1019, 2001

ROLE OF ADAPTIVE PLASTICITY IN RECOVERY OF FUNCTION AFTER DAMAGE TO MOTOR CORTEX

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Accepted 18 January 2001

Following a stroke or other source of injury to the motor cortex, movement deficits are common in the upper and/or lower extremity contralateral to the injury. Deficits include paralysis or weakness, abnormal muscle tone, abnormal posture, abnormal movement synergies, and loss of interjoint coordination.[20,144,217,223] Although dexterity with the impaired hand may be permanently affected, significant recovery occurs during the first several weeks after the injury (Fig. 1). Recovery is generally thought not to continue past 6 months; the ultimate outcome is largely a function of the initial severity of the deficit.[36,37]

Specific hypotheses regarding mechanisms underlying recovery of motor function after injury to the sensorimotor cortex are now beginning to emerge. At least part of the recovery process undoubtedly involves resolution of pathophysiologic events associated with cortical injury. However, over the past decade, neurophysiologic and neuroanatomic studies in animals, and neuroimaging and other noninvasive mapping studies in humans, have provided substantial evidence that the adult cerebral cortex is capable of significant functional plasticity. Furthermore, results from both human and animal studies are converging to suggest that postinjury behavioral experience is a major modulator of neurophysiologic and neuroanatomic changes that take place in the undamaged tissue. To the extent that neuroplasticity can contribute to restitution of function after cortical injury, it is important to understand the phenomena and underlying mechanisms

Abbreviations: AMPA, aminomethylisoxazole propionate; bFGF, basic fibroblast growth factor; CFA, caudal forelimb area; D-AMP, D-amphetamine; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; ICMS, intracortical microstimulation; LTD, long-term depression; LTP, long-term potentiation; M1, primary motor cortex; NMDA, *N*-methyl-D-aspartate; OP-1, osteogenic protein-1; PET, positron emission tomography; RFA, rostral forelimb area; TMS, transcranial magnetic stimulation

Key words: motor cortex; physical therapy; plasticity; rehabilitation; stroke

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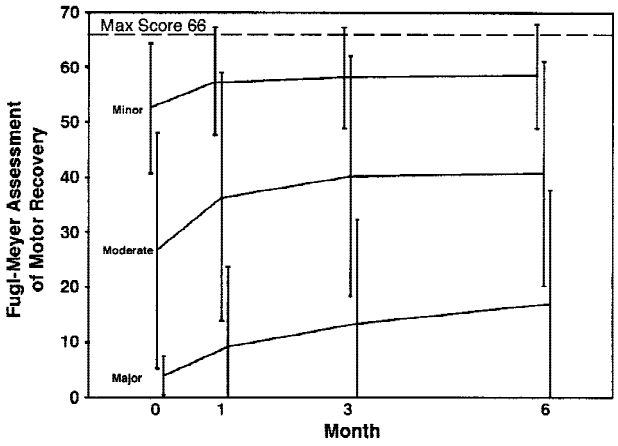

FIGURE 1. Poststroke recovery profiles for three different levels of stroke severity. Graph depicts means and 1 SD of Fugl–Meyer upper extermity scores after stroke in 459 individuals enrolled in the Kansas City Stroke Study.[37] Patients with different levels of stroke severity show different probabilities of recovery. (Reprinted from *Neuropharmacology,* Vol 39, Duncan, PW, Lai, SM, Keighley, J, Defining post-stroke recovery: implications for design and interpretation of drug trials, pp 835–841. Copyright 2000, with permission from Elsevier Science.)

at the synaptic, cellular, and systems levels of organization.

The goal of the present review is to summarize findings to date on physiologic and neuroanatomic plasticity in the motor cortex that occur following cortical injury. Although a large literature now exists regarding such plasticity in immature brains (e.g., see review by Kolb and Whishaw[118]), the present review will focus primarily on adults. Because of its importance in normal motor control, and because it is often involved in stroke or other cortical injuries, this review is restricted primarily to neural plasticity following injury to the primary motor cortex.

THEORIES OF RECOVERY

The theoretical framework for understanding recovery of function is still evolving after over a century of study as reviewed elsewhere.[2,132,203] According to one hypothesis described by von Monakow at the beginning of the twentieth century,[221] the function of remote cortical tissue is temporarily suppressed after focal cortical injury. This process is known as diaschisis. Recovery is thought to result from the gradual reversal of diaschisis. Contemporary studies of brain metabolism after cortical injury have largely confirmed that resolution of diaschisis is likely to play a role in functional recovery.[41,198] However, as more specific injury-induced events at distant sites are examined, it is becoming evident that: (a) diaschisis may persist for long periods of time after injury, that is, after significant recovery has occurred[88]; and (b) persistent remote effects of cortical injury are more complex than previously thought, and include disinhibition and hyperexcitability in addition to the well-known hypometabolism and inhibition.[3]

In addition to the resolution of diaschisis, motor recovery after cortical injury occurs in large part through behavioral compensation, rather than via "true recovery" or restitution of "normal" motor strategies.[47,53,203,232] For example, in one recent study of stroke patients, severely to moderately impaired subjects used more compensatory strategies with the trunk to accomplish a pointing task.[20] This is not unlike the response of rats after unilateral sensorimotor cortex lesions that employ postural compensation in retrieving food, rather than reestablishing normal motor strategies.[232] It has also been reported that original motor strategies can, in some cases, be regained after motor cortex injuries in primates.[53] However, this more complete recovery occurred after very small microinfarcts that resulted in mild and transient deficits in motor performance.

Although resolution of diaschisis (and other pathologic sequelae) and behavioral compensation play major roles in the phenomenon of motor recovery, it has also been suggested that other cortical (or subcortical) structures, either adjacent to or remote from the damaged area can "take over" the function of the damaged area. This theory, known as vicariation of function,[142] has gained considerable popularity over the past decade due to several recent examples of functional plasticity after cortical injury.[243] The degree to which the reorganization observed in spared tissue represents mechanisms related to restitution of the original function, behavioral compensation, or both, is still not entirely clear. However, a large number of recent studies are beginning to shed light on this issue and are reviewed in what follows.

FUNCTIONAL ORGANIZATION OF MOTOR CORTEX

The primate motor cortex, located in the precentral gyrus, is classically defined as the portion of the cerebral cortex that requires the least amount of electrical stimulation to evoke movement of skeletal muscles. In primate species, including humans, the so-called "motor cortex" is subdivided into several distinct regions based on anatomic, physiologic, or functional criteria. These regions include the primary motor cortex, the premotor cortex, the supplementary motor area, and the cingulate motor area (Fig. 2).[169,172,236,242] There is now evidence that at least some of these motor areas can be subdivided into even smaller components.[58,172,173,212] A com-

plete review of the findings related to neuronal plasticity from all motor cortical regions is beyond the scope of this presentation. For brevity, most of the data described in what follows will focus on primary motor cortex, or M1.

Electrical stimulation of M1 has revealed that different parts of the body are represented at different locations. The global topography of these representations follows an orderly progression from the hindlimb at the most medial locations, through the trunk, forelimb, and finally the face (and oral cavity) in the most lateral locations (Fig. 2). This arrangement was described in detail by Penfield over 50 years ago based on stimulation of the cortex of neurosurgical patients using surface electrodes and is usually referred to as the motor homunculus or motor map.[167,168] The classic depiction of the homunculus suggests that each part of the body is represented at a single specific location within M1, and that there is a steady progression from one body part to the next across the cortex.[230,240,241] Modern cortical mapping studies using intracortical microstimulation (ICMS) in nonhuman primates,[67,242] as well as recent neuroimaging studies in human subjects [27,69,139,177,188] have replicated this basic homuncular somatotopy in M1.

Although a global segregation of body parts is generally evident in functional maps of M1, it is now recognized that the representations of individual movements are widely distributed and overlapping in the motor cortex.[187,192] The orderly progression implied by the motor homunculus breaks down within each somatotopic subregion. For example, within the cortex devoted to the representation of the upper extremity, there is no clear arrangement of movements of the individual digits, wrist, forearm, elbow, or shoulder; instead, these representations are intermingled in a complex mosaical pattern. Furthermore, individual movements are represented at multiple, spatially discontiguous locations within the forelimb region.[6,33,67,124,133,147,156,171,202,204,205,237] In studies where electromyographic (EMG) activity has been recorded in conjunction with ICMS, representations of individual muscles have been found at multiple cortical locations, and individual muscle representations overlap those of other muscles.[33,35,83,159] Furthermore, by examining spike-triggered averaging of EMG activity in awake, behaving monkeys, it has been demonstrated that individual cortical neurons in motor cortex make monosynaptic connections with several motoneuron pools.[46,134] Finally, local cortical regions containing multiple, overlapping representations communicate via a dense network of intrinsic, horizontal connections.[85,86,111,112,229]

Several studies in human subjects using contemporary mapping techniques have also demonstrated a distributed organization. Using transcranial magnetic stimulation (TMS), a noninvasive technique in which a focused magnetic field pulse is used to gen-

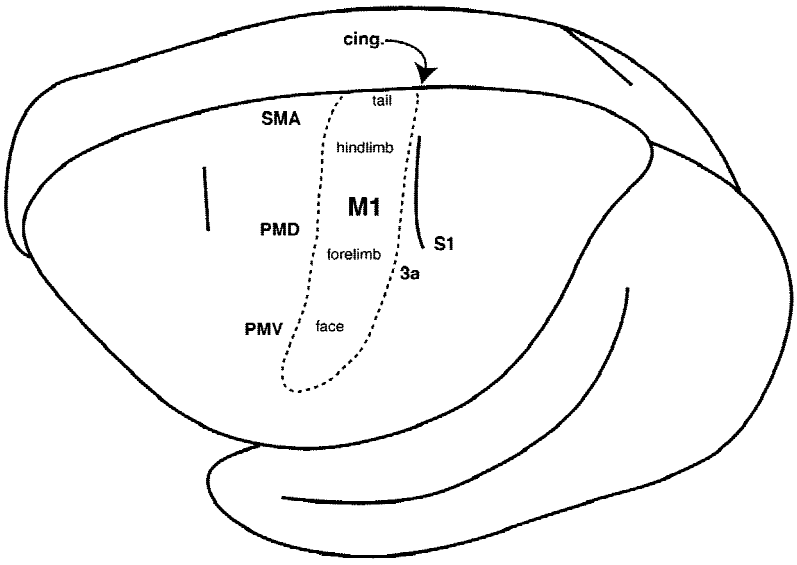

FIGURE 2. Location of motor areas in the frontal cortex of squirrel monkeys. At least five separate motor areas can be identified in this and other primate species. These include the primary motor cortex (M1), the supplementary motor area (SMA), the dorsal premotor area (PMD), the ventral premotor area (PMV), and the cingulate motor area. In turn, some of these motor areas can be divided further (e.g., into rostral and caudal subdivisions). This arrangement is similar in other primates studied to date, although the cortical sulci are much deeper in most other primate species (including humans). (Reprinted by permission from Academic Press.[159])

erate an electrical discharge in cortical neurons, multiple and overlapping representations for movements of the arm and hand have been revealed.[26] Functional neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), also suggest that the representations of individual arm, hand, and finger movements are multiple and overlapping[27,69,177,188] (also, see review by Schieber and Hibbard[193]). For example, individual finger representations have been shown to overlap each other[188] as well as the representations of the wrist and elbow.[177,188] It has been suggested that the somatotopic gradients superimposed across a largely distributed representation may account for observed patterns of separate and overlapping representations.[192]

In summary, the functional organization of the primate M1 is much more complex than has been classically described. Muscle representations overlap extensively; individual muscle and joint representations are re-represented within the motor map; individual corticospinal neurons diverge to multiple motoneuron pools; horizontal fibers interconnect distributed representations. This complex organization may provide the substrate for functional plasticity in motor cortex, at least within each local subregion.

ADAPTIVE PLASTICITY OF M1 AS A RESULT OF EXPERIENCE

Animal Studies. For nearly two decades, investigations of cortical plasticity in adult animals have utilized neurophysiologic techniques to demonstrate the mutability of functional activity in sensory and motor cortex. The invasive methods used in animal subjects have permitted examination of plastic changes at a variety of levels, including reorganization of representational maps, alterations in the activity of single or small groups of neurons, in vitro studies of altered synaptic function, and anatomic changes in neuronal structure. For example, in the early 1980s, using microelectrode recording techniques to define receptive fields of neurons in the somatosensory cortex, it was demonstrated that representations of the hand are altered by sensory experience. After experimental amputation of a digit of the hand, the representation of that digit is replaced by representations of adjacent digits.[137,138] Behavioral training procedures can also result in alterations in somatosensory maps. The representations of skin surfaces that are stimulated during a sensorimotor task are greatly expanded, and receptive field sizes are reduced.[94,178]

As in somatosensory cortex, representational maps in motor cortex also can be altered by a variety of manipulations, including changes in afferent sensory inputs, repetitive cortical stimulation, and pharmacologic manipulation.[154,187] Prolonged alteration of tactile and proprioceptive inputs and the associated muscle targets has been shown to produce plastic changes in motor maps in rats. If the forelimb is amputated in either perinatal or adult rats, the vibrissae and shoulder representations expand into the former forelimb territory.[34,189] Conversely, cutting the facial nerve causes a rapid increase in size of the adjacent forelimb representation (Fig. 3).[33,85,186,189] Alteration of proprioceptive inputs by adjusting the posture of specific joints can produce changes in the size of the forelimb representation, as well as changes in the specific movements evoked by stimulation.[190]

Artificial manipulations can also rapidly alter the organization of motor representations. The forelimb representation expands into the former vibrissa representation after prolonged electrical stimulation of the forelimb region in rat motor cortex,[155] a phenomenon similar to one observed at the beginning of the 20th century by Graham Brown and Sherrington.[70] A similar result was obtained following application of a gamma-aminobutyric acid (GABA) antagonist (bicuculine) into the forelimb representation, which resulted in an expansion of forelimb representations into the vibrissa representation.[90]

Plastic reorganization of motor maps in M1 can also be produced by alterations in motor behavior. Interhemispheric differences in the size and complexity of the hand representation in monkey M1 has been correlated with laterality of handedness, suggesting that natural behavior can affect the organization of cortical representations.[156] Motor learning paradigms, in which monkeys were trained to retrieve food pellets from a small well[158,170] or rats were trained to retrieve food pellets from a rotating disk,[114] resulted in a reorganization of movement representations in motor cortex. The representations of specific movements that were used to successfully perform the motor task were selectively expanded in the motor cortex at the expense of other forelimb representations. In contrast, repetitive unskilled movements that were used as motor activity controls and that did not exhibit evidence of motor learning did not produce changes in motor representations in rat or monkey motor cortex.[114,170] This suggests that only specific patterns of recently

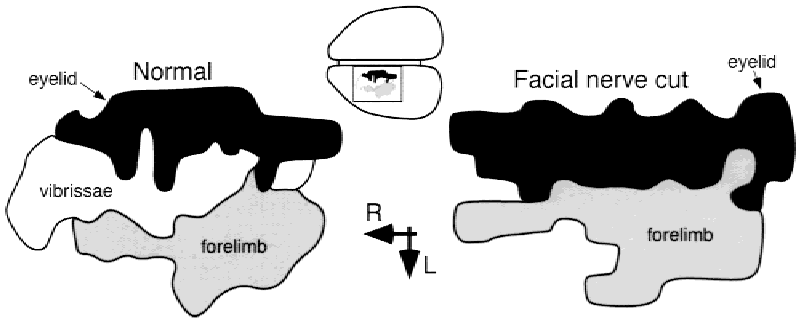

FIGURE 3. Alterations in motor representations after facial nerve transection in rats. Representations were defined by microelectrode stimulation in the motor cortex of anesthetized rats. In normal rats (left), the forelimb representation was separated from the eyelid representation by the vibrissa representation. Two weeks after a facial nerve transection (right), the forelimb and vibrissa representations were contiguous. Redrawn from an article by Sanes et al.[186] These experiments, and others like them, demonstrate that motor representations are modified by experience.

learned motor behavior are capable of producing functional plasticity in motor cortex.

Human Studies. Recent advances in imaging technology have permitted investigators to examine dynamic changes in human brain function. Of particular interest is whether this cortical activity is modulated as a function of learning and experience, as has been demonstrated in animal models.

Several studies of sensorimotor cortex suggest that functional activity can be altered in humans by chronic experience. In somatosensory cortex, the representation of the digits of the skilled hand is expanded in string musicians and blind Braille readers compared to the unskilled hand.[38,165] In motor cortex, the representation of the fingers of the skilled hand is reorganized in trained badminton players compared to the unskilled hand and to the representations in untrained players.[166] Together, these studies indicate that long-term practice of a particular sensorimotor skill can produce functional reorganization in relevant cortical representations.

There are several studies in humans that demonstrate functional reorganization associated with motor learning over much briefer time periods. On the whole, these studies indicate that motor cortex has the potential for rapid and large-scale functional changes in response to motor skill learning. Maps of motor outputs from M1 defined using transcranial magnetic stimulation (TMS) have been shown to change after brief periods of motor training. Repeated paired movements of the thumb with movements of the shoulder,[25] face,[24] or foot[130] produced a shift in the location of the thumb map toward the representation of the paired movement (i.e., a medial shift with shoulder or foot pairings, and a lateral shift with face pairings). Performance of unpaired movements did not affect the location of the thumb map. However, repeated practice of a single, specific movement can affect its cortical representation. Thumb movements made in a direction opposite to the movement direction evoked by TMS prior to training produced a progressive shift in TMS-evoked thumb responses toward the trained direction.[22] This effect manifested within 30 minutes, and was reversed within 30 minutes after training was halted.

Motor sequence learning has been shown to produce changes in M1 activity. Subjects either practiced a known sequence of finger movements,[84,106,107,164] or performed cued movements of individual fingers in an initially unknown repeated sequence.[163,244] Repetitive practice of a known movement sequence caused a progressive expansion of finger representations in M1 within 30 minutes,[84] over several days,[164] and over several weeks[107] as the sequence was learned. Map expansions paralleled improvements in motor performance. Karni et al. found that the differential activation of M1 for learned versus control sequences persisted for at least 8 weeks after training had stopped.[107] Repetitive, cued performance of an unknown movement sequence produced a decrease in reaction time to the cue, suggesting an implicit learning process, and a concurrent expansion of finger representations in M1.[163,244] Control sequences (i.e., without a repeated pattern) did not affect the map. Once explicit knowledge of the sequence was achieved, the map returned to its original size, presumably reflecting a difference in cognitive processing mechanisms for implicit versus explicit motor performance.

Several studies using positron emission tomography in human subjects have demonstrated activity changes in motor cortical structures, and in particular primary motor cortex, during the acquisition of new motor skills.[68,110,196,201,218,235] For example, Grafton et al.[68] studied subjects as they learned to

track a moving target with their hand. As accuracy increased and smooth pursuit movements developed, a parallel, progressive increase in M1 activation was detected, beyond activity levels related to movement performance. Learning-dependent increases in activation within M1 may occur in regions distinct from those activated by movement execution.[110]

Some studies have failed to demonstrate substantial changes in M1 during learning.[54,92] For example, Jenkins et al. found no difference in activity in sensorimotor cortex during the performance of a prelearned sequence versus learning of a novel sequence.[92] It should be noted, however, that subjects in this study were attempting to deduce the correct sequence via a trial-and-error process. This kind of sequence learning relies more on cognitive processing and less on strictly movement-related processing, such as correctly tapping the thumb to a particular finger[196,198] or smoothly tracking a moving target with the hand.[68] Thus, the specific skills being learned or practiced may critically determine the degree of M1 functional plasticity.

Mechanisms of Learning-Dependent Plasticity in Motor Cortex. One mechanism that has been suggested for mediating functional changes in the cerebral cortex is modification of the synaptic strength of horizontal connections. The most widely studied model of synaptic mechanisms underlying learning and memory comprises the phenomena of long-term potentiation (LTP) and long-term depression (LTD) in the rat hippocampus or cerebral cortex. Recent studies in slice preparations of rat motor cortex report that LTP and LTD can be induced in layer II/III horizontal connections,[76–80] similar to extensive studies in hippocampal slice preparations.[9] More recently, it has been demonstrated that both LTP and LTD can be induced in the neocortex of the freely moving rat, but multiple, spaced stimulation sessions are required.[55,214]

Recent results show that LTP induction in neocortex is associated with alterations in dendrite morphology and increased spine density, similar to those found in rats exposed to complex environments.[89] Furthermore, in postmortem slice preparations after motor learning, rats have larger amplitude field potentials in the motor cortex contralateral to the trained forelimb.[182] At the cellular level, several studies indicate that motor learning can produce changes in functional activity of neurons in motor cortex. Single-unit recording studies in awake, behaving animals have demonstrated altered neural activity in motor cortex in relation to skill acquisition in monkeys[1,56,57,140] and rats,[126] as well as associative conditioning in cats.[4,5,135] Together, these studies suggest that the synaptic strength of horizontal connections in the motor cortex are modifiable and may provide a substrate for altering the topography of cortical motor maps during the acquisition of motor skills.

The close correspondence between acquisition of new motor skills and alterations in the physiology of motor cortex circuitry is now becoming firmly established. However, if motor cortex map physiology in some way reflects the long-term storage of newly acquired motor programs, then alterations of neuronal morphology would also be expected (Fig. 4). It is now well established that major changes in neuronal structure occur in intact animals as a consequence of experience and learning. Early work showed that rats raised in complex environments had greater brain weight, thicker cortical tissue, greater neuron size, a greater degree of dendritic branching, higher dendritic spine frequency, larger synaptic contacts, more perforated synapses, and more synapses per neuron.[8,31,32,60,141,184,215,219,231] These results were later extended to adults.[15,71,97,102,183] Other studies demonstrated that the dendritic and synaptic morphology of motor cortex neurons was altered by motor learning tasks. For example, apical dendritic branching increased in layer V pyramidal neurons of sensorimotor cortex (contralateral to the trained forelimb) in adult rats trained for several days on a reach training task.[72,116,238] The number of synapses per neuron in layer II/III of the rat sensorimotor cortex increased after acrobatic training. Paralleling neurophysiologic results that showed no map changes without motor learning,[170] synaptic changes did not occur in a motor control group that traversed an obstacle-free runway.[115] Acrobatic training also results in an increase in layer V synapses per neuron[100,115] and an increase in the number of synapses per neuron formed by multiple synaptic boutons (axonal boutons that form synaptic connections with two or more postsynaptic processes).[100] The latter process has been implicated in changes in synaptic efficacy.[99]

Learning-dependent synaptogenesis appears to be specific to the cortical area undergoing physiologic reorganization. A recent study has demonstrated that rats trained on a skilled reaching task exhibited an expansion of the distal forelimb representations in the caudal (CFA), but not the rostral forelimb area (RFA).[114] Paralleling these physiologic results in these same animals, increases in the number of synapses per neuron within layer V were found only in the CFA, not in the RFA.[113]

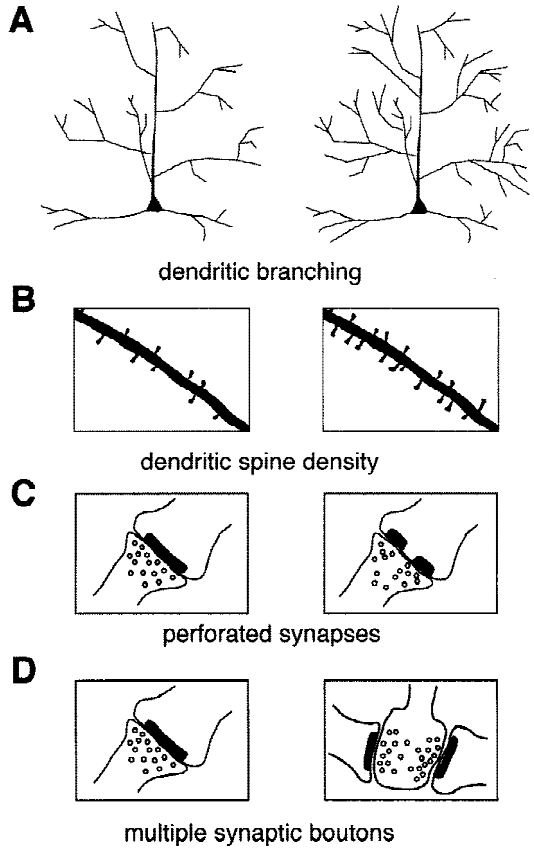

FIGURE 4. Changes in neuronal morphology after motor skill learning in rats. Several experiments have demonsrated increased dendritic branching **(A)**, increased dendritic spine density **(B)**, increased numbers of synapses per neuron (not shown), increased numbers of perforated synapses **(C)**, and increased numbers of synapses with multiple synaptic boutons **(D)** in the motor cortex of adult rats. These alterations occur either after environmental enrichment or the learning of specific motor tasks. Many of these same morphologic changes have now been demonstrated in intact cortical tissue after neuronal injury in rats. Such morphologic change may play a role in recovery of motor function after damage to motor cortex.

ADAPTIVE PLASTICITY OF M1 AFTER CORTICAL DAMAGE

Animal Studies. Because of the dynamic capacity of the sensorimotor cortex that has been demonstrated in numerous studies after behavioral training, peripheral nerve injury, or cortical stimulation, it is not unexpected that these same cortical areas undergo considerable changes in functional organization following cortical injury. Effects remote from the site of injury are not surprising given that neurons in any damaged region of cortex have reciprocal synaptic connections with neurons in other brain regions. Direct investigation of this question using cortical stimulation techniques has been undertaken since early in the 20th century. In 1917, Leyton and Sherrington published results from ablation of the arm area in chimpanzees.[127] The M1 arm area was first identified using surface stimulation techniques. Then the area yielding movements of thumb, fingers, wrist, and elbow was excised. Significant paresis was observed in the hand contralateral to the lesion during the initial week after the lesion. However, after 1 month, significant recovery of movement was observed in the affected hand. When the motor cortex was reexamined using stimulation techniques, no movements of the hand could be obtained by stimulation of the adjacent, intact cortical tissue. Leyton and Sherrington concluded that there was no evidence that the undamaged arm area assumed the function of the damaged hand area.

During the next 30 years, several investigators examined the behavioral consequences of lesions in motor cortex of a variety of mammals, including primates. However, no direct evidence of vicarious function by intact cortical areas was reported, despite a number of ablation–behavior experiments that utilized stimulation mapping techniques.[125] Then, in 1950, Glees and Cole used surface stimulation techniques in monkeys and reported that after ablating the thumb area of primary motor cortex, the thumb representation reappeared in the adjacent, intact motor cortex.[59] There was little interest in similar studies of functional reorganization after focal injury until the resurgence of plasticity experiments in the mid-1980s.

Recent studies using intracortical microstimulation techniques have more firmly established that cortical motor represention are alterable after cortical injury. In these studies in adult monkeys, microstimulation techniques were used to define the topographic representation of the upper extremity. Motor maps were derived in great detail by using interpenetration distances of approximately 250 μm. Then microlesions were made affecting only about 30% of the hand representation. Hand movement representations in the adjacent, undamaged cortex (spared representations) were tracked for several months after the microlesion. If monkeys were allowed to recover spontaneously, that is, without any post-lesion behavioral training or encouragement to use the affected limb, the remaining, undamaged hand representation was decreased in size (Fig. 5).[157] At sites where stimulation evoked digit and wrist movements before the infarct, stimulation now evoked movements of the proximal musculature (i.e., elbow and shoulder). At 1 month post-lesion, the total spared hand representation is reduced by more than half. A gradual recovery occurred over the ensuing months, but full recovery of the motor map was rarely achieved. Hand areas of spontane-

ously recovering monkeys were approximately 75% of their original areas after 4 months.[52]

Because it has long been suggested that physical therapeutic interventions might improve recovery after injury to motor cortex,[95,96,161] additional studies have examined the effects of post-lesion motor training on recovery of motor maps. In these experiments, monkeys were placed in restraint jackets that restricted the use of the unimpaired limb.[160] Daily repetitive training procedures were employed to encourage improvement in manual skill. After manual skill had returned to normal levels, the motor cortex was reexamined with microstimulation techniques. In contrast to spontaneously recovering monkeys, the monkeys that received postinjury behavioral training showed retention of the undamaged hand representations (Fig. 5). On average, there was a net *gain* of approximately 10% in the total hand area adjacent to the lesion. More recently, it has been shown that the retention of hand area adjacent to a microlesion in M1 requires repetitive behavioral training, because use of the restraint jacket alone resulted in no change in hand representations beyond that which was seen with spontaneous recovery.[52] Hand representations in monkeys that wore the restraint jacket continuously for up to 1 year were only 80% of the pre-lesion area.

It should be noted that in the primate studies to date, it has not been possible to demonstrate differences in motor abilities as a function of post-infarct experience.[52] Although the reasons are not yet entirely clear, it is likely that the small numbers of animals per group combined with large individual variability in motor performance may have contributed to the lack of evidence for behavioral differences. It is also possible that the measure of motor skill used in these studies (numbers of finger flexions required to retrieve a food pellet from a small well) was insensitive to subtle differences in behavior among the groups. Finally, because of the small size of these microinfarcts (30% of the primary motor cortex hand area), all of the animals may have been able to compensate relatively quickly for mild motor deficits. Additional studies examining a variety of motor skills after larger cortical infarcts are needed to address this issue more directly. In any event, it is clear that despite variability in behavioral outcomes after microinfarcts in motor cortex, the changes in neurophysiologically derived maps are consistent, and can be modulated in predictable ways by postinjury experience.

Further evidence that reorganization of intact, adjacent cortical tissue contributes to functional recovery has come from similar motor mapping studies

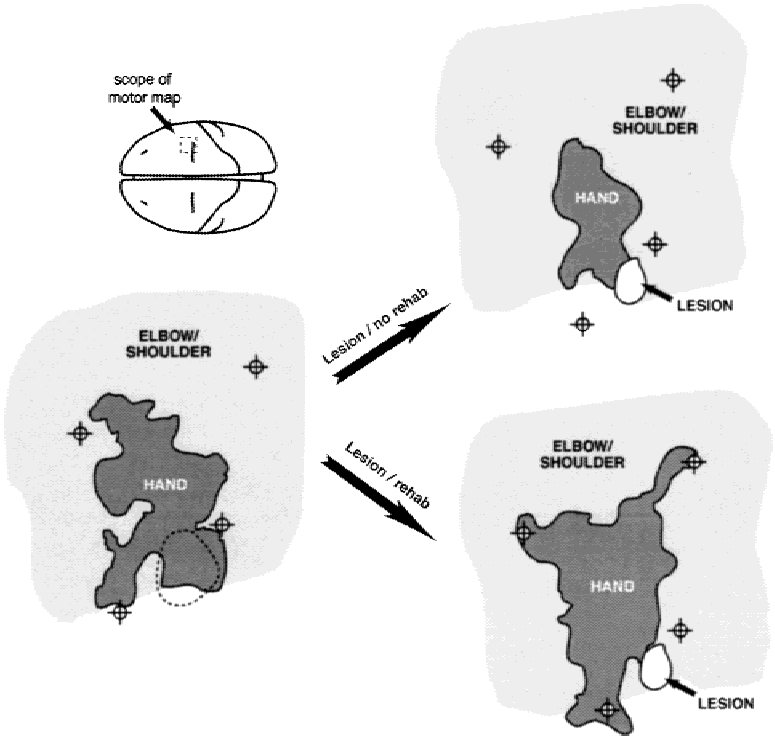

FIGURE 5. Summary of functional remodeling of the hand representation in primary motor cortex after a stroke-like injury. Data were derived from hundreds of microelectrode penetrations using microstimulation techniques to determine evoked movements in anesthetized monkeys. These studies, and others like them, demonstrate that the uninjured tissue adjacent to a cortical injury undergoes functional reorganization that can be modulated by postinjury behavioral training. (Reprinted by permission from Stockton Press.[153])

in rats. In these studies, after bilateral ablation of the forelimb area in rat motor cortex, motor performance was impaired. However, recovery occurred if electrical stimulation of the ventral tegmental nucleus was paired with forelimb responses.[12] The stimulation is thought to have played a motivational role in encouraging forelimb use. When the motor cortex was reexamined following recovery, a novel forelimb representation appeared caudal and lateral to the ablated representation.[13] The size of this representation was directly related to the behavioral performance of the recovered animals. Finally, ablation of the newly emerged forelimb representation resulted in reinstatement of the deficit.

Recent results in monkeys suggest that, at least after large lesions of the primary motor cortex, more remote cortical motor areas may participate in recovery. After unilateral damage to the M1 hand area and subsequent recovery, the GABA agonist, muscimol, was injected into various intact motor regions to induce transient inactivation. Whereas inactivation of M1 of the injured or intact side had no effect, inactivation of the premotor cortex of the injured hemisphere rapidly reinstated the deficit.[131] Functional alterations have also been reported in the supplementary motor area after M1 lesions.[1] Thus, after damage to M1, other motor areas in the injured hemisphere may contribute to recovery of motor skills.

Although the focus of this review is on motor cortical areas, postinjury reorganization has also been observed in somatosensory cortex after similar injuries. Following a small infarct in the primary somatosensory (area 3b) hand representation in monkeys, the injured digit representations reemerge in adjacent, intact tissue.[93] In addition, representations of the affected digits expand in other somatosensory areas, such as areas 3a and 1.[243] Taken together, these recent findings in both somatosensory and motor cortex provide substantial evidence that vicariation of function occurs in intact cortical regions after cortical injury.

Human Studies. Several noninvasive techniques have been used in humans to examine the effects of cortical injury on the function of intact cortical tissue. Subjects are typically those with cortical lesions (either ischemic or hemorrhagic) or lacunar subcortical lesions involving the internal capsule. These recent studies have used noninvasive techniques for mapping the functional organization of the injured cortex, such as positron emission tomography, functional magnetic resonance imaging, transcranial magnetic stimulation, and magnetoencephalography. Although the location of the injury is frequently unknown or uncontrolled, these studies have consistently shown that functional changes occur in several cortical areas after stroke or other cortical damage, paralleling results from animal experiments. As this review of functional plasticity after cortical injury in humans is not exhaustive, the reader is referred to the more complete review by Cramer and Bastings.[28]

Using transcranial magnetic stimulation, it has been shown that, shortly after stroke, the excitability of the motor cortex is reduced, and the cortical representation of the affected muscles is decreased.[19,213] It is likely that this effect occurs from a combination of diaschisis-like effects[220] and disuse of the affected limb.[130] Peri-lesional changes in cortical activity have been shown to occur using a variety of techniques.[23,29,105,200] Furthermore, after 8–10 weeks of rehabilitation treatment, there was an enlargement of the motor map in the injured hemisphere relative to the initial postinjury map.[213] Still further, constraint-induced movement therapy, in which the unimpaired hand is constrained for 2 weeks to induce goal-directed movement with the impaired hand, produces a significant enlargement of the representation of the paretic limb.[128,129,228] These results closely parallel the results of rehabilitative training of the impaired hand in primate studies described earlier.[160]

It has also been shown repeatedly that, after recovery, movement of the recovered hand was associated with increased bilateral activation of remote brain areas, such as the cerebellum, and premotor cortex, as well as the sensorimotor cortex.[18,51,148,226,227] Interestingly, these increased activations often have occurred in the sensorimotor cortex of the uninjured hemisphere after good recovery, leading many to speculate that the uninjured hemisphere plays a significant role in recovery.[10,149,199] However, the role of mirror movements in these studies is still unclear.[227] The role of reorganization in the intact hemisphere has also been questioned because the presence of ipsilateral motor evoked potentials after stimulation of the nonstroke hemisphere (using TMS) has been associated with poor motor outcome.[150,216] Clearly, the role of the uninjured hemisphere after stroke requires further study.[29]

SUBSTRATES FOR FUNCTIONAL SUBSTITUTION

Anatomic Changes Associated with Cortical Injury. Several recent studies have provided evidence that adaptive alterations occur in the anatomy of surviving cortical and subcortical neurons. Because morphologic changes are known to be associated with motor learning, it is plausible that the same or simi-

lar changes in intact cortical structures may contribute to motor recovery after cortical injury.

Studies of anatomic changes after unilateral cortical injury have been conducted almost exclusively in rats. After injury to the sensorimotor cortex, rats preferentially use the forelimb ipsilateral to the lesion for postural support, reaching, and forelimb placing.[7,11,101,103,233,234] This asymmetry is seen within 1 or 2 days after the lesion, is maximal during the first 2 weeks post-lesion, and persists for at least 1 month.[101,103] Thus, it is not surprising that compensatory anatomic changes occur in the intact sensorimotor cortex contralateral to the injury.

Because the processes involved in changes on the two sides of the brain differ, especially with respect to the influence of postinjury behavioral experience, these two topics will be discussed separately. Because most of these studies have focused on the contralateral (uninjured) hemisphere, these studies will be discussed first. Then, we review the evidence for similar changes in the injured hemisphere.

Contralateral (Uninjured) Side. Unilateral damage to the sensorimotor cortex in rats results in a number of time-dependent anatomic alterations in the motor cortex opposite the side of the lesion. The homotopic cortex opposite sensorimotor cortex lesions undergoes a two-phase process of use-dependent dendritic overgrowth, followed by elimination of dendrites in layer V.[99,103,104,119,122] Beginning a few days after injury, dendritic branching in layer V neurons begins to increase, reaching its peak at day 18. This increase is primarily in higher-order branches.[103,104] At this timepoint, the volume of dendritic processes in layer V is significantly increased.[101] At 10 days post-lesion, myelinated axons are reduced in volume fraction.[99] At 30 days post-lesion, dendritic branching begins to decrease, suggesting that dendritic pruning has occurred. However, branching is still elevated above normal levels. At this time, the number of synapses and the surface area of dendritic membrane per layer V neuron are increased significantly.[101] In addition to synaptic density, the proportion of synapses formed by multiple synaptic boutons and perforated postsynaptic densities is significantly elevated at 30 days post-lesion, but not at 10 or 18 days. Single synapse numbers per neuron do not increase.[99] Together, these results suggest that after unilateral sensorimotor cortex lesions, a period of dendritic growth is followed by dendritic pruning, synapse formation, and changes in the specific structure of synaptic connections. The recent findings that the fine structure of synapses changes after injury is of particularly interest, because several studies in other systems have suggested that these ultrastructural changes are related to changes in synaptic efficacy.[102,151,225] Other studies suggest that the pruning phase is associated with adaptive changes as well. The administration of the *N*-methyl-D-aspartate (NMDA) receptor antagonists MK-801 or ethanol during a critical period after cortical injury can block the pruning process, and disrupt behavioral recovery.[119,121]

There is also evidence that these anatomic changes are dependent upon the increased use of the unimpaired forelimb. After lesions, rats compensate by relying more heavily on the unimpaired limb for postural support.[103] If the unimpaired forelimb is immobilized during the period of dendritic overgrowth (0–15 days post-lesion), dendritic arborization does not occur in the intact hemisphere and behavioral performance is further degraded.[104] Dendritic overgrowth is not affected by immobilization of the impaired forelimb. Thus, dendritic overgrowth is closely related to the time of overreliance on the unimpaired forelimb, whereas the subsequent dendritic pruning is related to a return of more symmetric use of the forelimbs. Dendritic overgrowth does not occur after immobilization in sham-operated animals, indicating that the magnitude of morphologic changes results from an interaction of the lesion and post-lesion behavior.[104] Finally, motor skill training for 28 days after the lesion significantly increased layer V synapses per neuron.[100] Cortical lesions may therefore trigger the events that lead to use-dependent cortical plasticity in regions interconnected with the damaged cortical area. It is concluded that the changes in the intact cortex are an interactive effect of the lesion and post-lesion behavior.

Other studies appear to contradict these studies of use-dependent growth in the intact hemisphere. After cortical aspiration lesions, increased use of the intact forelimb was not associated with an increase in dendritic arborization of identified corticospinal neurons.[174] Also, after either small electrolytic or more extensive aspiration lesions, no evidence of a use-dependent increase in dendritic aborization was found in the intact hemisphere.[50] Both of these negative results were obtained at 18 days post-lesion, the peak of dendritic overgrowth in the previous studies. The authors of the latter two investigations proposed several possible factors that might contribute to the discrepancy, including differences in lesion methodology. More recent data confirmed that the dendritic growth does not occur after aspiration lesions, or after electrolytic lesions followed by aspiration (T. A. Jones, personal communication and see

Voorhies and Jones[222]). Furthermore, electrolytic lesions may fail to produce dendritic growth if they are too small, a potential factor in some of the negative results with electrolytic lesions.[101] Although the mechanisms controlling this phenomenon are not yet fully understood, it is clear that, under certain conditions, use-dependent dendritic overgrowth occurs in the intact hemisphere after motor cortex damage. This effect appears to depend upon the presence of the damaged tissue, and is more likely to occur after large cortical lesions.

Ipsilateral (Injured) Side. Indirect evidence suggests that anatomic changes occur in the uninjured cortical tissue surrounding the injury. After focal cortical ischemia in rats, GAP-43 immunoreactivity increased in the surrounding tissue, suggesting axonal sprouting.[207] In addition, synaptophysin immunoreactivity is increased in the surrounding tissue, suggesting an increase in the number of synapses in the intact cortex.[206] It is of interest to note that the GAP-43 increase was significantly elevated only at early survival times (3, 7, and 14 days), whereas the synaptophysin increase was significant at later survival times (14, 30, and 60 days), suggesting that axonal sprouting was followed by synaptogenesis.[208]

After injury to the sensorimotor cortex in rats, extreme use of the affected limb can result in an enlargement of the lesion and further motor impairment.[120] If the unimpaired limb is placed in a restrictive cast after cortical injury, rats must rely heavily on the impaired limb for posture and locomotion. Forced overuse of the impaired limb during the first week after injury results in expansion of the injury and poorer motor performance.[82] Forced overuse during the next 7 days does not result in injury expansion, but nonetheless results in poorer motor performance. This study strongly suggests that there are specific vulnerable periods for maladaptive effects of use after injury. Timing of these maladaptive effects must be considered along with timing of adaptive effects in any rational therapeutic design for treatment of motor deficits after injury.

In contrast, acrobatic motor training after a similar injury in rats resulted in no detectable increase in the size of the lesion and improved motor performance.[100] It would appear that the behavioral conditions that follow cortical motor injury are critical in neural processes underlying recovery. The specific conditions that contribute to adaptive plasticity versus those that contribute to maladaptive plasticity are now beginning to come to light.

Subcortical Changes Several lines of evidence suggest that the reorganization seen in motor cortical maps (as well as somatosensory maps) has a substrate at the cortical level. However, at least in the somatosensory system, it is likely that reorganization occurs at several levels of the neuraxis after injury. For example, after massive sensory loss, as might occur after amputation, reorganization has been reported at cortical levels, in the thalamus, in the dorsal column nuclei of the brainstem, and in the spinal cord.[49,98] It has recently been shown that, at least after long-term amputation, significant sprouting occurs at the level of the brainstem that might account for massive reorganization in somatosensory cortex. Normally, afferents from the face terminate in the face representation of the trigeminal nucleus. However, 10 years after an amputation, some of these afferents sprout new connections to terminate in the cuneate nucleus, normally the recepient of afferents from the arm.[91] The growth of face afferents into the deafferented cuneate nucelus in the brainstem appears to contribute substantially to the activation of hand cortex by face afferents.

Despite the growing evidence for subcortical changes in somatosensory structures following amputation, similar data from subcortical motor structures are rare. Mechanisms of cortical reorganization after amputation were recently addressed using transcranial magnetic stimulation techniques and then testing intracortical inhibition and facilitation.[16] The results suggest that after amputation, motor reorganization occurs predominantly at cortical levels. It is important for future studies to assess directly the contribution of functional and structural plasticity in the motor system (e.g., red nucleus, spinal cord, etc.) after peripheral or central injury.

A few studies have now examined plasticity in subcortical motor structures in adult animal models. After thermocoagulatory lesions and injection of anterograde tracers into the uninjured hemisphere, labeled fibers were found in the striatum of injured animals contralateral to the injection (i.e., ipsilateral to the injury), suggesting that cortical neurons may undergo axonal sprouting following an injury to the cortex.[17,146] Unusual ultrastructural details have been observed in the newly formed synapses of the deafferented striatum.[17] These changes are associated with a variety of changes in gene expression and growth-promoting factors.[211] It is of interest to note that, as with studies of morphologic changes in the homotopic, intact cerebral cortex discussed previously, if aspiration lesions are made, the sprouting and several growth-related cellular changes are not found.[145]

A large number of studies have reported unusual corticofugal projections after neonatal sensorimotor cortex lesions, including corticorubral, corticopon-

tine, and corticospinal projections.[12,143,185] However, evidence for widespread axonal sprouting or synaptic remodeling in these subcortical pathways is still weak in injury models in adult mammals.

In summary, unilateral brain injury can trigger compensatory mechanisms, whereby neurons in the intact tissue are induced to sprout new connections. At least some of this compensatory growth requires behavioral pressure.

Changes in Neuronal Excitability and Neurotransmitter Regulation after Cortical Injury. Only recently have long-term changes in specific neurotransmitter systems been investigated in chronic cortical injury. These studies are important because they may lead to new intervention strategies and potential pharmacologic treatment of chronic stroke.

Changes in two neurotransmitter systems, GABA and glutamate, have been implicated in behavioral deficits following stroke, and alterations in the activity of each may play a role in functional recovery. Behavioral deficits similar to those seen after stroke are found in primates after reversible inactivation of primary motor (M1) and premotor cortex by injection of the $GABA_A$ agonist muscimol.[123,194] There is a decrease in the density of inhibitory $GABA_A$ receptors and an increase in hyperexcitability in the area adjacent to the lesion following cortical injury in the rat.[195] This hyperexcitability has been observed up to 4 months after the lesion. Others studies have shown a bihemispheric reduction of $GABA_A$ receptors in multiple cortical areas connectionally related to the damaged area in rats.[176] Bilateral reductions in inhibitory $GABA_A$ receptors and concurrent bilateral increases in excitatory glutamate NMDA receptors occur in spared areas of cortex for up to 4 weeks after middle cerebral artery occlusion in mice.[175] A similar reduction of $GABA_A$ receptors and increase in NMDA receptors occurs in the ipsilateral thalamic nucleus projecting to the damaged areas of cortex.[175]

A recent study has shown differential downregulation of $GABA_A$ receptor subunits in peri-infarct and remote areas after focal cortical infarcts in rats.[179] Alterations in subunit composition are associated with changes in electrophysiologic and pharmacologic properties of $GABA_A$ receptors, and these changes may be of importance for functional cortical reorganization after injury.[179,180]

Immunohistochemistry of the peri-infarct region in rats has shown that 1 week after injury, parvalbumin-positive interneurons (presumably GABAergic) show signs of degeneration and a reduction in the number of dendrites.[152] There is also a reduction in the number of parvalbumin-positive neurons immediately adjacent to the lesion. These results suggest that the downregulation of the GABAergic system, resulting in a decrease in inhibition, also occurs presynaptically.

An upregulation of NMDA receptors in cortex following ischemic lesion appears to be a consistent result in rodents. Other glutamatergic receptors, the aminomethylisoxasole propionate (AMPA) and kainate receptors, have been shown to slightly increase in density in the peri-infarct region, although not significantly.[175] Significant changes in the density of AMPA and kainate receptors were not seen in remote areas of cortex away from the lesion.[175]

Changes in GABA and glutamate receptor densities may explain increased hyperexcitability following a lesion. Excitability changes in intact tissue following cortical injury have traditionally been thought to be pathologic, and thus maladaptive. However, evidence is now accumulating to suggest that excitability changes may be one aspect of postlesion adaptation in the neuronal network after injury. For example, pharmacologic studies have shown that drugs that enhance the effect of GABA result in the potentiation of behavioral deficits following cortical lesion in rats.[191] Conversely, drugs that attenuate the effect of GABA speed up the recovery of function following cortical lesion.[75] These results suggest that a downregulation of inhibitory GABA receptors may be an adaptive response to injury, and that a certain degree of hyperexcitability may favor recovery, at least in rodents.

Regulation of specific neurotransmitter systems may play a critical role in the functional reorganizational process that occurs subsequent to cortical injury in primates (see earlier sections). Perhaps the natural response to injury is a decrease in GABA inhibition that acts to unmask latent horizontal connections.[90,182] Glutamate is the major neurotransmitter of the horizontal connections in cortex, and any synaptic modifications that may be necessary for functional reorganization may be mediated by NMDA receptors.[76]

GABA and glutamate receptor density in primate cortex following injury has yet to be examined. Changes in neurotransmitter systems have not yet been studied in relation to functional reorganization following skilled training in primates. The remote effects of cortical ischemia are believed to be caused by alterations due to electrical or chemical signals emanating from the infarct, alterations along connectivity patterns (diaschisis) and use-dependent adaptations (see Witte and Stoll[239] for review). Intact brain areas that are remote from, but contribute in-

formation to, a damaged motor area may undergo substantial anatomic and neurochemical changes. It is possible that these alterations may contribute to adaptive changes for recovery of lost function, and for learning-dependent plasticity in intact animals.

MODULATION OF MOTOR RECOVERY BY PHARMACOLOGIC TREATMENT

The extent of functional recovery after brain injury can also be modulated by use of drugs.[61] In addition to the well-known effects of certain drugs administered acutely after injury that act as neuroprotective agents, thereby limiting the extent of neuronal damage,[162] other agents have been found to be effective during the longer period of recovery. For example, the role of norepinephrine in recovery from brain injury has been well documented.[62] After cortical injury in rats, administration of D-amphetamine (D-AMP) enhances motor recovery, at least in part, by enhancing norepinephrine release.[44]

Growth factors also have been proposed to enhance neurologic recovery after cortical injury.[48] In rats, nerve growth factor (NGF), basic fibroblast growth factor (bFGF), and osteogenic protein-1 (OP-1) have recently been found to enhance recovery of sensorimotor function.[108,109,117] Although efficient delivery of these substances to the central nervous system in humans poses a significant obstacle, it is likely that future recovery strategies will utilize a combination of physical therapeutic and pharmacotherapeutic approaches.

Effects of Amphetamine on Recovery after Stroke. Certain pharmacologic agents, such as D-AMP, promote recovery after stroke, but their effects are optimized only when delivered in combination with behavioral training.[64] The seminal study that generated interest in amphetamine-facilitated recovery of function has been attributed to Feeney and colleagues.[39] Rats were given a unilateral lesion of motor cortex. Locomotion was assessed by the ability of the injured animals to traverse a wooden beam suspended above a table. The results demonstrated that nontreated rats spontaneously recovered from brain injury. However, the rate of recovery was enhanced in rats that were required to traverse the beam while under the influence of D-AMP. A number of subsequent studies have extended these results.[39,40,42,43,45,63,64,66,87,197,210] The results indicate that a tight coupling between behavioral experience and D-AMP intoxication is necessary for optimal recovery. Importantly, these effects have been found with a single dose of D-AMP and post-lesion practice.[65]

Success with these animal studies has led to several clinical studies in which stroke patients have been administered D-AMP followed by physical therapy.[21,30,63,81,181,224] In all but one study[181] this combined treatment regimen has improved outcome beyond what was expected. These studies are encouraging, indicating that the results from the animal studies cited earlier are applicable to clinical situations.

Although this research has successfully demonstrated the beneficial effects of combining behavioral training with D-AMP treatment, several issues are unresolved. The neural mechanisms underlying the therapeutic facilitation of recovery of function are still relatively unknown. Does combining behavior with D-AMP lead to anatomic changes that initiate and/or maintain recovery? Another issue concerns the temporal parameters for optimal therapeutic outcome. Is there a therapeutic window for the use of behavioral training combined with D-AMP treatment?

Mechanism of Action of Amphetamine on Recovery after Cortical Damage. D-AMP is believed to mediate recovery from cortical damage by activating the noradrenergic system.[40] One of the several pharmacologic actions of D-AMP is to stimulate release of norepinephrine from terminals or varicosities along the axons and block its reuptake, thereby prolonging an increase in noradrenergic activation of postsynaptic receptors. Noradrenergic axons project profusely throughout the cortex. Release of norepinephrine from these ubiquitous projections has a neuromodulatory effect upon cortical neurons. Norepinephrine, like other neuromodulators, is thought to enhance signal-to-noise input to sensory neurons and, in general, facilitates a neuron's response to nonoptimal signals.[73] This phenomenon is ideal for experience-based plasticity[74,136] and therefore may account for the enhanced recovery from cortical damage associated with pairing behavioral experience with D-AMP intoxication.

Although the effects of D-AMP are realized soon after treatment begins, there is evidence that long-term structural changes are also associated with combining behavioral experience with D-AMP treatment. Stroemer et al.[209] found a significant correlation between the expression of GAP-43 (a protein associated with axonal growth) and synaptophysin (a protein associated with synaptogenesis) with functional recovery of forelimb use following a middle cerebral artery occlusion in rats (also see Stroemer et al.[208]) This important observation suggests that D-AMP may facilitate the formation of new synaptic connections

within cerebral cortex, thereby playing a key role in mechanisms of functional recovery after cortical injury.

SUMMARY AND CONCLUSIONS

The primary motor cortex forms a distributed network in which muscles and movements are represented at multiple locations within a local region. This distributed organization forms a substrate that is amenable to use-dependent alteration of outputs via modulation of local synaptic processes. Based on investigations of adaptive plasticity phenomena over the past 15–20 years, it must be concluded that the motor cortex of adult mammals can undergo widespread changes in functional organization as a result of behavioral experience and central or peripheral injury. In particular, the motor cortex is altered during the acquisition of new motor skills such that the muscles and movements engaged in the skilled activity come to be represented over greater cortical territories. These changes in functional topography are accompanied by anatomic alterations, such as increases in synaptic number.

In addition, the organization of motor cortex is now known to be altered following cortical injury, as might occur in stroke. Both human and animal studies have demonstrated both acute and chronic changes in functional topography and anatomy of intact cortical tissue adjacent to the injury, and of more remote cortical areas, including those of the contralateral (uninjured hemisphere). Of considerable importance for rehabilitative sciences is the demonstration that behavioral experience and cortical injury interact such that motor use can adaptively modulate the plasticity process that inevitably occurs after cortical injury. The recent findings of acute and chronic alterations in neurotransmitter regulation after injury may provide a basis for new pharmacologic targets for stroke recovery.

This work was supported by NIH grants from NINDS (NS30853), a center grant from the NIA (Kansas Claude D. Pepper Center for Independence in Older Americans), the KUMC Training Program in Biomedical Research, and a center grant from NICHD (HD02528).

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