

## ADAPTIVE PLASTICITY IN MOTOR CORTEX: IMPLICATIONS FOR REHABILITATION AFTER BRAIN INJURY

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**It is now widely recognized that the cerebral cortex of adult human and non-human mammals is capable of widespread functional and structural plasticity. During the learning of new skills, cortical regions associated with sensorimotor function of the body parts most utilized for the skilled task come to be represented over larger cortical territories. More recent studies have shown that functional and structural changes take place in the cerebral cortex after injury, such as occurs after stroke or trauma. These two modulators of cortical function, sensorimotor learning and cortical injury, interact. Thus, after cortical injury, the structure and function of undamaged parts of the brain are remodeled during recovery, shaped by the sensorimotor experiences of the individual in the weeks to months following injury. These recent neuroscientific findings suggest that new rehabilitative interventions, both physiotherapeutic and pharmacotherapeutic, may have benefit via modulation of neuroplastic mechanisms.**

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### INTRODUCTION

Over the past decade, progress in two research fields has fostered a new, evidence-based paradigm in neurobiology and rehabilitation. First, neuroscientific studies demonstrating functional plasticity in the cerebral cortex, initially developed in the 1980s in animal models, have matured to the point that some of the underlying anatomic, physiologic, and biochemical mechanisms are now becoming clear. In turn, this has allowed the generation of specific hypotheses regarding potential treatment approaches. Second, an abundance of neuroimaging data from human stroke populations has provided evidence that animal results can be generalized to humans. Additionally, alterations in cortical function that take place in the chronic period after stroke are likely to be quite widespread, and not simply confined to the peri-infarct regions.

As a result, scientists and clinicians alike have begun to consider seriously the development of treatment strategies that are initiated long after stroke has occurred. The challenge of acute

treatment after stroke to preserve vulnerable tissue is still critical. However, the concept that cortical functions can be restored long after stroke survivors have reached a plateau in their recovery has given hope to clinicians and scientists alike that significant improvement in motor function can be achieved even when acute neuroprotection is not feasible.

### SKILL-DEPENDENT PLASTICITY IN UNINJURED MOTOR CORTEX

The past decade has brought an increasingly refined understanding of the neural bases for functional plasticity in the cerebral cortex. A large number of studies in human and animal models have demonstrated that the cerebral cortex is modifiable by various behavioral manipulations or peripheral nerve pathology (1). After motor skill learning in normal animals, the topography of representations in motor cortex is altered. Movements that are used in the newly learned task are represented over larger cortical territories (2–5).

It now appears that repetitive motor activity alone is not sufficient to produce representational plasticity in cortical motor maps. When monkeys were trained to retrieve food pellets from a very small well, requiring skilled use of the digits, progressive increments in motor performance were seen over a period of about 10 days. Monkeys trained to retrieve pellets from a larger food well displayed accurate performance from the beginning of training; that is, no additional skill was required. In the two groups, the total number of finger flexions was matched. Comparisons between pretraining and posttraining maps of cortical movement representations revealed no task-related changes in the cortical area devoted to the hand in the large well group. Movement specific changes in the small well group were large and consistent, and corresponded to the actual movement kinematics of the task. It would appear that repetitive motor activity alone does not produce functional reorganization of cortical maps. Instead, motor skill acquisition, or motor learning, is a prerequisite factor in driving representational plasticity in motor cortex (6). Consistent with these results, it was recently shown that the development of skilled forelimb movements, but not increased forelimb strength, was associated with a reorganization of forelimb movement representations within rat motor cortex (7).

In another recent study examining the concordance between neurophysiologic and synaptic changes induced by skill learning, it was found that in comparison to rats in a motor activity control group, rats trained on a skilled reaching task exhibited an

areal expansion of wrist and digit movement representations within the motor cortex. No expansion of hindlimb representations was seen. This functional reorganization was restricted to the caudal forelimb area, as no differences in the topography of movement representations were observed within the rostral forelimb area. Paralleling the physiological changes, trained animals also had significantly more synapses per neuron than controls within layer V of the caudal forelimb area. No differences in the number of synapses per neuron were found in either the rostral forelimb or hindlimb areas. This study provides support for the co-occurrence of functional and structural plasticity within the same cortical regions and provides strong evidence that synapse formation may play a role in supporting learning-dependent changes in cortical function (8). While exercise can alter the thickness of motor cortex (9), it is unclear what elements are responsible. Based on studies in the cerebellum, it is likely that at least some of the volumetric increase with motor activity is due to angiogenesis (10, 11).

Skill learning is also accompanied by increased synaptic density within layer II/III of motor cortex (12). At least in barrel cortex of rats, modification of local N-methyl-D-aspartic acid (NMDA) receptors is necessary for experience-dependent plasticity (13).

Based on physiological recordings from slice preparations in rats, it now appears that the synaptic strengths in horizontal connections in motor cortex can be modified, forming a putative substrate for altering the topography of cortical motor maps. For example, in rat motor cortex, long-term potentiation (LTP) and long-term depression can be induced in layer II/III horizontal connections (14–16). More recently, after motor training, rats were found to display larger amplitude field potentials in the motor cortex contralateral to the trained forelimb (17, 18). The amount of LTP that could be induced in layer II/III horizontal connections in the trained motor cortex was less than in controls. In addition, LTP induction alters the morphology of layer III pyramidal neurons. Increased spine density and changes in dendritic morphology are observed, not unlike those seen after exposure to complex environments (19). Interestingly, experimentally induced seizure activity in rats (kindling) results in increased synaptic strength and an enhanced area of polysynaptic field potentials. In addition, this manipulation results in a doubling of the size of cortical motor representations (20).

#### ADAPTIVE PLASTICITY IN INJURED BRAINS: POTENTIAL NEURAL SUBSTRATES FOR REHABILITATIVE TREATMENT

If changes in synaptic strength in horizontal connections and synaptogenesis can underlie functional modifications in motor cortex of normal animals during motor skill learning, it follows that these same mechanisms may play a role in recovery after damage to motor cortex. While most studies of recovery have

been based on large lesions of the motor cortex, involving the entire primary motor cortex (M1) representation, some studies have employed relatively small, or focal, lesions to examine changes in cortical representations in adjacent, undamaged tissue. For example, after focal lesions in the primary somatosensory cortex hand area, monkeys gradually reacquire sensorimotor skill. This recovery is accompanied by reemergence of the injured fingertip representation (21). A similar phenomenon has been found after focal lesions in the M1 hand area. Movement representations are altered in the cortex adjacent to the lesion, but the details of the topographic reorganization depend on the type of post-lesion training experienced by the animal. In the absence of training, spared finger representations undergo a further reduction in territorial extent. With daily repetitive training after the injury, spared finger representations are retained, suggesting a role for the adjacent undamaged cortex in recovery, and a direct influence of training on cortical plasticity mechanisms (22–24).

Post-infarct training also appears to result in changes in neuroanatomic structure. A combination of environmental enrichment with daily skilled-reach training in post-ischemic rats resulted in enhanced dendritic arborization within layer V of the undamaged cortex (25).

M1 is not the only cortical region controlling motor output. Motor representations can be found in other cortical areas, such as the premotor cortex, the supplementary motor area, and cingulate motor cortex (e.g. 26). Since neurons in these additional motor areas, like those in M1, send projections to the spinal cord (27), it is possible that alterations in the structure and function of non-primary motor areas partially underlie recovery. Recent studies suggest that the premotor cortex ipsilateral to the injury may play an important role. A study in monkeys by Liu & Rouiller (28) provides direct evidence for the role of the premotor cortex in recovery from lesions in M1. After physiologic identification of the M1 hand area, lesions were made by injection of ibotenic acid. Functional recovery occurred over a period of 3–4 months. Then spared regions of the damaged and intact hemisphere were transiently inactivated by injection of muscimol. While inactivation of intact tissue in M1 in either hemisphere had no effect, inactivation of premotor cortex on the injured hemisphere reinstated the deficit in manual dexterity.

Further, it appears that the premotor cortex is physiologically and anatomically altered by damage to M1. In monkeys, the ventral premotor hand representation expands after damage to the hand representation in M1. The amount of expansion is proportional to the amount of ischemic damage to M1 (29). Also, such M1 infarcts result in alterations of axonal projections from ventral premotor cortex. Since the normal target of these axons, M1, has been damaged, many of these axons terminate in novel cortical regions, including the somatosensory cortex. As M1 normally forms reciprocal connections with the somatosensory cortex, it is possible that premotor cortex acts vicariously to assume functions of the damaged M1 (30). Interestingly, recent clinical data also implicates the premotor cortex in recovery after stroke (31, 32).

In addition to alterations in axonal trajectories, other widespread structural changes also occur after injury to motor cortex. In rats, 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 (33–35). At the peak of dendritic overgrowth (day 18 post-injury), synaptic density within layer V and spine density on layer V pyramidal neurons are normal. At a later time point, when dendritic pruning has already begun to occur (day 30), synaptic density and spine density are significantly increased. These results suggest that dendritic growth precedes synapse formation. In the perilesional zone, immunocytochemical evidence is also suggestive of dendritic sprouting and synaptogenesis (36, 37).

Hypotheses regarding putative synaptic mechanisms for functional plasticity after injury are now developing. Small photothrombotic lesions in somatosensory cortex of rats result in excitability changes in remote brain areas associated with a downregulation of GABAA receptors in the perilesional zone, a phenomenon lasting for weeks (38). Similar events occur after middle cerebral artery occlusion (39). This dysfunction in the GABAergic system is associated with facilitation of LTP (40). In addition, cortical injury results in enhancement of NMDA receptors in the perilesional zone (39). Thus, regulation of both excitatory and inhibitory neurotransmitters in the cerebral cortex may play a critical role in the reorganizational process that occurs subsequent to focal cortical injury.

#### PROSPECTS FOR NEW REHABILITATIVE INTERVENTIONS AFTER STROKE IN HUMANS

Since the structure and function of the cerebral cortex are modifiable after injury, putative treatments that attempt to maximize neuroplasticity are becoming increasingly popular. Paralleling the behavioral interventions in animal studies, several human studies have now shown that intensive practice with the impaired limb (constraint-induced movement therapy, or CI therapy) can result in further recovery in stroke patients, even though they had previously reached a plateau (41). Both transcranial magnetic stimulation and functional magnetic resonance imaging studies now have shown that functional plasticity in motor cortex accompanies recovery associated with CI therapy. Changes include expansion of the hand representation after training, and increased activation in the ipsilateral cortex, including the peri-lesional cortex (42, 43).

The extent of functional recovery after brain injury can also be modulated by use of drugs (44). 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 (45), others have been found to be effective during the longer period of recovery, presumably by their effects on specific neurotransmitter systems. For example, the role of norepinephrine in recovery from brain injury has been well documented (46). After cortical injury in rats, administration of amphetamine en-

hances motor recovery, at least in part, by enhancing norepinephrine release (47). In addition, amphetamine administration is associated with neural sprouting and synaptogenesis (37). In human stroke patients, amphetamine may also result in improvement in motor performance (48, 49). Modulation of neurotransmitter systems after cortical injury is a provocative approach that has significant potential utility.

Growth factors have also been proposed to enhance neurologic recovery after cortical injury (50). In rats, nerve growth factor, basic fibroblast growth factor and osteogenic protein-1 recently have been found to enhance recovery of sensorimotor function (51–53). Finally, early investigations of the effects of human marrow stromal cells in rats after sensorimotor cortex injury have been promising. Significant recovery of function was coincident with increases in brain-derived neurotrophic factor and nerve growth factor (54). While 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 and pharmacotherapeutic approaches.

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