REVIEW

Training-induced Recovery of Manual Dexterity after a Lesion in the Motor Cortex

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Cerebral injury, such as stroke, cause functional deficits; however some functions can recover with postlesion rehabilitative training. Several recent studies using rodents and monkeys have reported the effects of postlesion training on functional recovery after brain injury. We present herein an overview of recent animal experimental studies on the effects of postlesion motor training on brain plasticity and motor recovery. Our study in the macaque monkey reported the effects of hand motor training on motor recovery after lesioning of the primary motor cortex (M1). In monkeys that had undergone intensive daily training after the lesion, manual dexterity recovered to previous levels. Relatively independent digit movements, including those of precision grip, were restored in the trained monkeys. While hand movements recovered to some extent in the monkeys without postlesion training, these monkeys frequently used alternative grips to grasp a small object instead of the precision grip. These findings suggest that recovery after M1 lesions includes both training-dependent and training-independent processes, and that recovery of precision grip requires intensive postlesion training. Recent results of both brain imaging and gene expression analyses suggest that functional and structural changes may occur in uninjured motor areas during recovery of hand function after M1 lesions. In particular, our preliminary results suggest that structural changes in ventral premotor cortex neurons may participate in functional compensation of precision grip. (Keio J Med 59 (1) : 4–9, March 2010)

***Keywords*: hand, neuronal plasticity, primates, recovery of function, rehabilitation**

Introduction

Some brain functions can recover following cerebral injury such as stroke, and appropriate rehabilitative training is thought to facilitate the process of recovery. However, it remains largely unclear how rehabilitative training promotes functional recovery. Several recent studies have reported the effects of postlesion training and large contributions have been made not only by clinical research using human patients[1–3] but also by basic research on rodents and monkeys. In this basic research, brain injury is artificially induced in a specific region of the animal brain, and recovery of function can then be examined under specific postlesion conditions. The extent of postlesion training-induced functional recovery can thus be determined. In addition, the underlying mechanisms can be investigated. Recently, brain imaging techniques such as functional magnetic resonance imaging (fMRI) have been applied to human stroke patients to investigate changes in brain activity during functional recovery.[4–9] However, using animal models of brain injury, it is possible to investigate both the molecular and anatomical basis of functional recovery in addition to changes in brain activity. Herein, we provide an overview of recent studies in which experimental animals were used to investigate the effects of postlesion rehabilitative training

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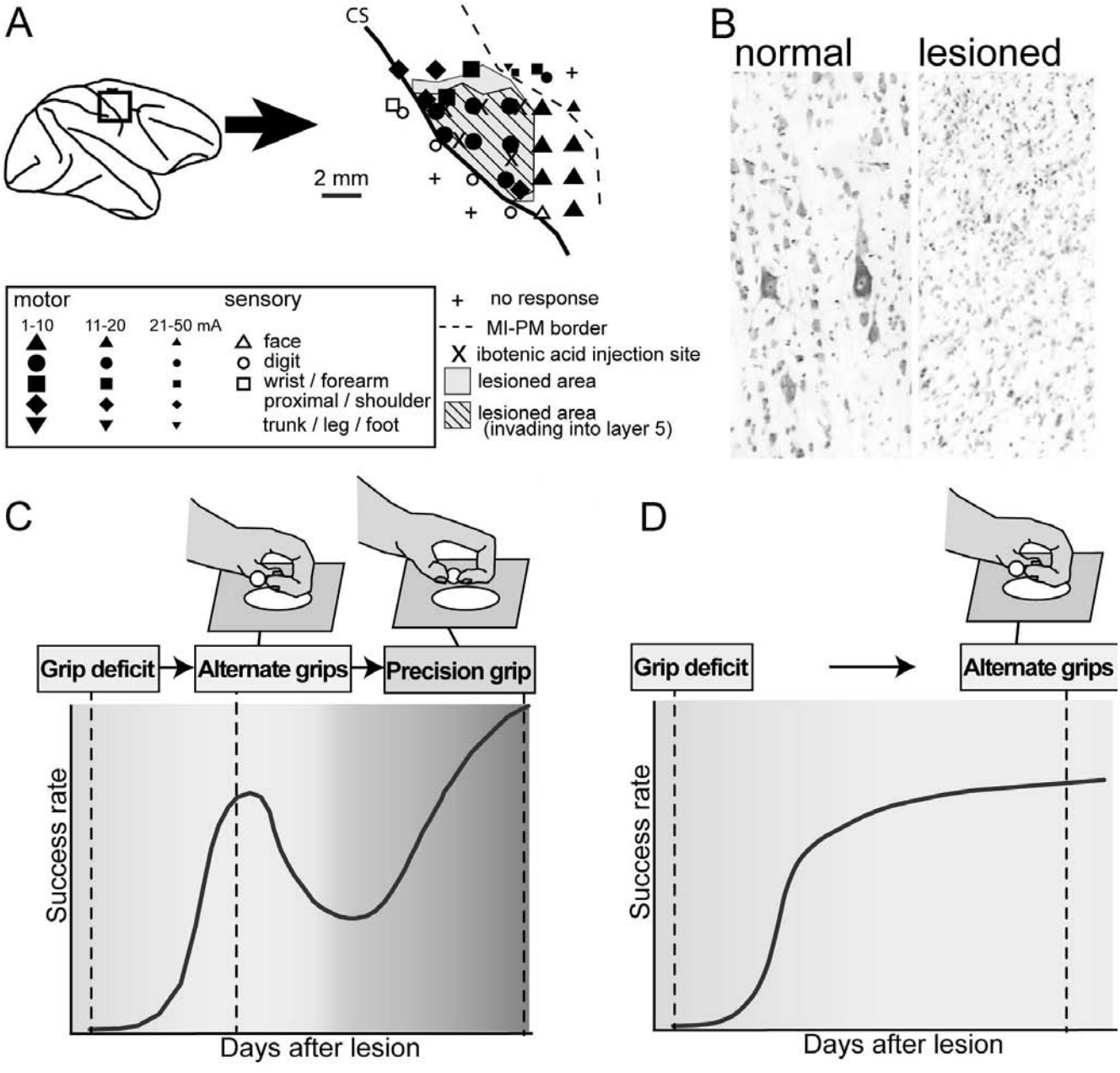

Fig. 1 (A) Lesioned areas superimposed on intracortical microstimulation (ICMS) maps of M1. Movements elicited at threshold and sensory responses to light tactile stimuli are indicated by symbols. Some electrode penetration sites yielded no responses to ICMS at current strengths up to 50 μA or to sensory stimulation. Hatching indicates areas of histologically confirmed lesions. Oblique lines within the hatching indicate that the lesion included layer 5, where efferent projections to the spinal cord originate.[42] Dotted lines indicate the presumed border between M1 and the premotor cortex, which were determined by movement thresholds, sulcal landmarks, and cytoarchitecture as visualized by Nissl staining.[43–45] CS: central sulcus. (B) Normal and ibotenic acid-lesioned areas of M1. Ibotenic acid injection resulted in loss of neurons and gliosis. (C) Schematic figure showing the relationship between change in rate of success and change in grip form in trained monkeys. While the monkeys could not retrieve the food pellets at all immediately after M1 lesions, their motor performance improved progressively during the post-lesion training period. In the middle of the recovery process, they frequently employed alternative grips, holding the food pellet between the tip of the index finger and around the proximal joint of the thumb. Thereafter, the precision grip was again employed. At the point when grip strategy changed, the monkeys frequently failed to retrieve the pellets because of inadequate coordination between digits. (D) In the untrained monkeys, many alternative grips, involving holding of the food pellet between the tip of the index finger and around the proximal joint of the thumb, were observed during the recovery period. In contrast to the trained monkeys, these alternative grips were not replaced by the precision grip. This figure is modified from our previous report (Murata Y, *et al*.: J Neurophysiol 2008; 99: 773-786).[17]

on brain plasticity and motor recovery.

Effects of Postlesion Training on Motor Recovery

Experimental studies using mice and rats have the advantage of availability of large numbers of subjects, thus many experiments have been conducted in such rodent models to elucidate the most effective training methods for functional recovery. For example, recovery of forelimb motor function was observed in brain-lesioned rats that had undergone motor training in object retrieval using the affected forelimb.[10] In contrast, similar recovery was not observed with full-body motion training using a running wheel.[10] Moreover, functional recovery was found to be promoted by a combination of rehabilitative motor training and electrical stimulation around the injured region of the brain.[11] Biernaskie, *et al*. conducted an experiment in rats to determine how efficacy of rehabilitation differs depending on when motor training commences. In this experiment, recovery of forelimb movements was compared among groups that began motor training 5, 14, or 30 days after lesioning of motor cortex. Level of recovery was highest in the group that had begun motor training 5 days after lesioning, the earliest commencement of the three groups.[12] In contrast, another study reported that movement immediately after brain injury increases the initial injury.[13] Excessive glutamate concentration has been implicated in this use-dependent increase in brain injury.[14–16] The findings of Biernaskie, *et al*. indicate that motor training immediately after injury has larger effects on functional recovery, probably because the increase in brain plasticity during this period induces functional reorganization of uninjured brain regions, despite increasing the initial injury.

We examined the process of functional recovery after brain injury in the macaque monkey, as it has cerebral and musculoskeletal structures similar to those of humans. We induced a lesion in the primary motor area (M1) of the cerebral cortex, from which a large portion of the motor output projections to the spinal cord originate, and examined the recovery of motor function.[17] Among motor functions, the recovery of dexterous hand function, a characteristic of some primate species such as humans, apes, and macaque monkeys, has been investigated in detail[18,19] because of its importance for human quality of life.

Initially, we examined the hand movements of the monkeys prior to lesion induction when retrieving small food pellets. Before lesioning, all monkeys retrieved the food pellet using a precision grip, with the index fingertip and thumb tip in finger-to-thumb opposition. We then mapped the motor representation in M1 using intracortical microstimulation techniques (**Fig. 1A**), in which a tungsten microelectrode was advanced into the motor cortex perpendicular to the cortical surface to a depth of 5 to 15 mm under ketamine anesthesia. Electrode penetrations were spaced at 2 mm intervals, and electrical microstimulation up to 50 μA was applied to evoke movement at each electrode penetration site. Ibotenic acid, a neurotoxic drug, was then injected intracortically to destroy the hand area of M1. In the ibotenic acid-injected region, irreversible loss of cortical neurons and proliferation of glial cells occurred (**Fig. 1B**). Immediately after lesion induction, paralysis, including complete loss of digit movements, was observed in the hand contralateral to the lesioned motor cortex. After the lesion, we divided the monkeys into two groups: those given intensive post-lesion motor training and those without any post-lesion training, and compared motor recovery in the two groups.

Over the first several weeks after lesioning, index finger movement followed by thumb movement were observed in both postlesion-trained and untrained monkeys. Postlesion training comprised intensive daily training (1 hour per day, 5 days per week) using a task involving retrieval of small food pellets from cylindrical wells. In postlesion trained monkeys, behavioral indices used to evaluate manual dexterity recovered to the same level as in the prelesion period after 1 or 2 months of training. Many alternative grip strategies, such as holding the food pellet between the tip of the index finger and around the proximal joint of the thumb, were observed during the middle stage of recovery (**Fig. 1C**). Over time, the location of the food pellet on the thumb changed from proximal (around the metacarpophalangeal joint) to distal (around the interphalangeal joint). During the subsequent period, which featured a transient decrease and then another increase in rate of success, use of the precision grip gradually increased (**Fig. 1C**). At 1 to 2 months after lesioning, precision grip was used as often as prior to lesioning. Thus, transfer from alternative grips to the precision grip occurred despite the transient decrease in rate of success in postlesion-trained monkeys.

Even in the postlesion-untrained monkeys, both success rate and hand movements recovered to some extent (**Fig. 1D**). Similar to the trained monkeys, the untrained monkeys used alternative grips for several weeks after lesioning; however, in contrast, alternative grips were not replaced by precision grip (**Fig. 1D**). These findings indicate that recovery includes both training-dependent and training-independent processes. In particular, the recovery of precision grip may be promoted by intensive postlesion motor training.

Mechanisms of Compensation Involved in Functional Recovery

Neuronal cells that have been lost do not regenerate when a mature brain is injured. It is therefore thought that some functional compensation occurs in uninjured cerebral regions as a basis for training-induced functional recovery. Several previous studies using rats and

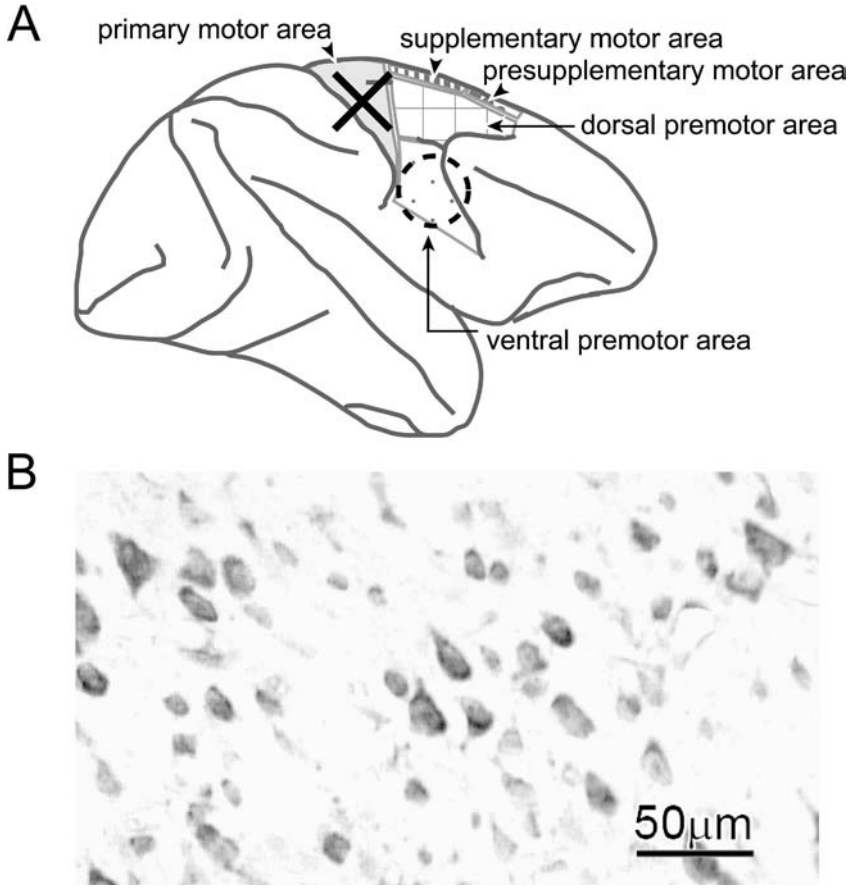

Fig. 2 (A) The five motor-related areas in cerebral cortex of the macaque monkey. The primate motor cortex is organized into distinct areas based on structural and functional criteria, which are hierarchically arranged to coordinate fine movements of the digits and limbs.[29–31] Among the motor areas, the primary motor area (M1) has the largest number of corticospinal connections, the motor output projections to the spinal cord. When M1 is injured, other motor areas are thought to compensate for the function of the injured area. Our preliminary results in a brain imaging study suggest that the ventral premotor area plays a role in compensation for dexterous hand movements (dotted line). (B) Example of mRNA expression of Growth-associated protein-43 (GAP-43). GAP-43 is one of the molecules whose expression has been found to be related to axonal sprouting and structural alteration of synapses.[32–34] Our recent findings indicate that mRNA expression of GAP-43 increased in the ventral premotor area during the recovery of hand function after M1 lesions.

squirrel monkeys reported that the functional motor representation map around the region of injury in the motor cortex changes with rehabilitative motor training.[20,21] These studies involved induced injury of the brain in the forelimb movement area of motor cortex, and showed that the forelimb area reappeared in the region surrounding the lesion during training-induced functional recovery. Another study also reported that the functional motor representation map in regions of cortex remote from injury changes during functional recovery if the region of brain injury is large.[22] It is thought that these changes in the motor representation map are involved in functional compensation after brain lesions. In addition, structural changes of neuronal cells have also been reported as the basis of functional compensation.[20,23–26] One study reported that rats with enriched rehabilitative training of the affected forelimb exhibited enhanced dendritic complexity and length of layer 5 pyramidal cells in motor cortex compared with those without postlesion training.[27] This is a remarkable example of the effects of postlesion motor training on the structure of neuronal cells.

As indicated above, our study showed that recovery of precision grip was observed in the macaque monkey with postlesion training even after most of the hand area in M1 had been lesioned. It is thought that M1 is required for precision grip,[28] and we confirmed that neurons in the ibotenic acid-injected region did not regenerate. Uninjured brain regions may thus have compensated for the function of the lesioned area in M1. In primate cerebral cortex, several motor-related cortical areas exist in addition to M1 (**Fig. 2A**),[29–31] and are candidate areas for functional compensation after M1 lesions. Changes in brain activity may be involved in this functional com-

pensation. To detect changes in brain activity, we performed a brain imaging study using positron emission tomography (PET) scanning with oxygen-15 labeled water, and measured regional blood flow in the brain, which is expected to increase with increased brain activity. We examined brain activity while monkeys performed a task involving precision grip in retrieving a small object from a slit. Preliminary results indicated that activity of the ventral premotor area increased during functional recovery after lesioning of M1.

We also examined reorganization of neural circuits, which may have occurred as the basis for the observed changes in brain activity. To investigate whether reorganization of neural circuits occurs during functional recovery, we focused on gene expression of plasticity-related molecules. Growth-associated protein-43 (GAP-43) is one of the molecules whose expression have been shown to be related to axonal sprouting and structural alteration of synapses.[32–34] Our previous studies indicated that this molecule plays important roles in memory function in the primate brain[35–40] and the development of sensory[41] and motor projections[38] (**Fig. 2B**). Our preliminary gene expression analysis suggests that GAP-43-mediated remodeling of axon terminals occurred during recovery, especially in the excitatory neurons of the ventral premotor area (**Fig. 2B**). The results of both brain imaging and gene expression analyses suggest that structural changes may occur in the ventral premotor cortex neurons after M1 lesions, and that premotor cortex neurons may participate in functional compensation for precision grip.

Future Perspectives

There have been only a small number of studies of the effects of postlesion rehabilitative training on functional recovery after brain injury, and further research is needed to clarify these effects. Because the central nervous system and musculoskeletal structures of rodents are quite different from those of primates, the importance of research using monkeys will increase in applying research findings to the clinical treatment of human patients. For example, as described above, an experiment was conducted to compare the efficacies of rehabilitative motor training initiated at different time points after injury of the brain in the rat.[12] It is important that similar experiments be conducted in monkey models of brain injury to determine the effects of early rehabilitation in primates.

Moreover, only fragmentary knowledge exists concerning the basis of training-induced functional recovery after brain injury, such as changes in the functional motor representation map of motor cortex and dendritic structures of neurons. Future studies at the level of neural circuits will be important in fully determining the mechanisms of functional recovery following brain injury. In particular, it will be important to understand how postlesion rehabilitative training induces the anatomical changes in the central nervous system that result in functional recovery. It will also be important to examine functional recovery at the molecular level, such as exploration of gene expression profiles by DNA microarray analysis. Although it is challenging to determine the changes that occur in the brain during functional recovery from the molecular to the behavioral level, this will no doubt yield findings of great clinical value.

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