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Review article

Effects of rehabilitative training o A review of animal studies

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ABSTRACT

Neuromotor systems have the capacity for functional recovery following damage to the central nervous system. This recovery can be enhanced by rehabilitative training. Animal studies in which artificial damage is induced in a specific region of the brain or spinal cord of rodents or monkeys have contributed to our understanding of the effects of rehabilitative training. In this article, I provide an overview of recent studies in which experimental animals were used to investigate the effects of rehabilitative training on motor recovery and brain plasticity. A study from my group in the macaque monkey reported the effects of hand motor training on motor recovery after lesioning of the primary motor cortex (M1) or the corticospinal tract at the cervical level. In monkeys that had undergone extensive post-lesion training, manual dexterity recovered to previous levels. Rehabilitative training was more effective in promoting recovery of manual dexterity when initiated immediately after the corticospinal tract lesion rather than 1 month later. Both functional brain imaging and gene expression analyses suggest that functional and structural changes may occur in undamaged motor areas during recovery of hand function after M1 or corticospinal tract lesions.

Contents

1. Introduction

Damage to the central nervous system (*i.e.*, brain or spinal cord) causes functional deficits. Not all functions are irreversibly lost, however, as some recover following the damage. Clinical experience and observations suggest that appropriate rehabilitative training facilitates the recovery process. However, the mechanisms by which rehabilitative training promotes functional recovery remain largely unclear. Recovery of hand movements after central nervous system injuries is an important issue because it is essential for the quality of human life; however, recovery of hand movements is known to be less than that of leg/foot function (Coupar et al., 2012; Twitchell, 1951). The neural mechanisms underlying recovery of hand movements have been investigated in human patients with stroke and spinal cord damage (*e.g.*, Lang and Schieber, 2004; Wade et al., 1983; Wenzelburger et al., 2005; Wittenberg and Schaechter, 2009). In addition, major contributions have been made in experimental studies with animals in which damage is artificially induced in a specific region of the brain or spinal cord, as I will discuss below. Animal studies are important not only for understanding the effects of rehabilitative training on recovery of function under defined conditions, but also for

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elucidating the neural mechanisms underlying training-induced recovery; they can be used to investigate changes associated with functional recovery, including those of gene/protein expression, anatomical structure, and brain activity. Here I provide an overview of recent studies in which experimental animals were used to investigate the effects of post-lesion rehabilitative training on forelimb/hand motor recovery and brain plasticity. In particular, I focus on our recent studies with a monkey model of brain or spinal cord damage.

2. Effects of rehabilitative training after cortical damage

Recovery of forelimb motor function has been investigated in rats in which the unilateral sensorimotor cortex was artificially damaged. Rats that had undergone motor training to retrieve an object by using the affected forelimb showed recovery of forelimb movements, whereas recovery of forelimb movements was poor when rats were given full-body motion training on a running wheel (Maldonado et al., 2008). Rehabilitative training of the affected forelimb combined with anti-inflammatory treatment strongly improved motor performance (Liebigt et al., 2012). These and other results in cortically damaged rats have provided important suggestions on how to design effective rehabilitative training for stroke patients. For example, determining the ideal timing for the onset of rehabilitative training after the damage is considered important for maximizing functional recovery. In a study conducted in cortically damaged rats to determine how the efficacy of rehabilitation depends on when rehabilitative motor training commences (Biernaskie et al., 2004), the recovery of forelimb movements was compared among rats in which motor training was initiated 5, 14, or 30 days after the lesion. The results showed that the level of recovery was highest in the group for which post-lesion training had begun the earliest (on day 5). In other studies, movements immediately after brain damage have been reported to exacerbate the initial damage, possibly because excessive glutamate release, which is known to be neurotoxic, occurs (Choi et al., 1987, 1988; Humm et al., 1999; Michaels and Rothman, 1990). Therefore, motor training immediately after cortical damage has larger effects on functional recovery, presumably because the increase in brain plasticity during this period induces functional reorganization of undamaged brain regions, and the benefits of training when the brain is plastic outweigh the risk of inducing extra damage.

Nonhuman primate models of brain damage are also important for bridging animal studies and human clinical studies, because the brain and body structure of are more similar across primate species than between primates and rodents (Alstermark et al., 2004; Courtine et al., 2007; Isa et al., 2007; Kuypers, 1982; Lemon, 2008). In some nonhuman primate species including Old World monkeys, dexterous hand function is as highly developed as in humans, and the recovery of hand movements has been investigated in cortically damaged monkeys (Passingham et al., 1983; Vilensky and Gilman, 2002). However, a disadvantage of experimenting with monkeys is the difficulty of conducting studies with a large number of subjects. Therefore, in monkey studies, the location and size of brain damage must be rigorously controlled. In addition, the behavioral environment should be strictly controlled to compare different experimental groups with relatively small numbers of subjects. We have investigated the effects of post-lesion rehabilitative training on hand motor recovery and brain plasticity in the macaque monkey, a genus of Old World monkeys that perform dexterous hand movements, including the use of a precision grip (holding a small object with an index finger-to-thumb opposition). In our monkey model of brain damage, a focal lesion is induced 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. We map the motor representation in M1 by using intracortical microstimulation (ICMS) techniques (Fig. 1a). Electrode penetrations are spaced at 2-mm intervals, and electrical microstimulation of up to 50 μA is applied to evoke movement. Ibotenic acid, a neurotoxic drug, is then injected intracortically to destroy the hand digit area of M1. This leads to irreversible loss of cortical neurons and proliferation of glial cells in the injected region (Fig. 1b). Subsequently, flaccid paralysis is observed in the hand contralateral to the lesioned M1.

By using this monkey model of focal M1 damage, we investigated the effects of rehabilitative motor training on the recovery of hand movements (Murata et al., 2008). We divided the M1-lesioned monkeys into two groups – those given post-lesion motor training and those without any post-lesion training- and compared motor recovery between the groups. The post-lesion training comprised intensive daily training (1 h per day, 5 days per week) on a task involving retrieval of small food pellets from cylindrical wells (Fig. 1c). This task, and another in which a small food morsel inserted into a vertical slit was retrieved (Fig. 1d), were used to evaluate manual skill.

Before the lesion, all of the monkeys retrieved food pellets by using a precision grip. In the monkeys that were given post-lesion training, behavioral indices used to evaluate manual dexterity recovered to the same level as in the pre-lesion period after 1 or 2 months of training. Many alternative grip strategies, which were different from the strategy observed before the lesion (*e.g.*, holding the food pellet between the tip of the index finger and around the proximal joint of the thumb) were observed during several weeks after lesioning (Fig. 2a). This is because independent digit movements, in which the thumb extends and the index finger flexes at the same time, was inadequate during the middle stage of recovery. During the subsequent period, the precision grip gradually increased in frequency and by 1–2 months after lesioning was used as often as it was before the lesion. Behavioral indices used to evaluate manual dexterity recovered to some extent in monkeys that were not given post-lesion training, although they were still lower than those before the lesion (Fig. 2b). Like the trained monkeys, the untrained monkeys used alternative grips during several weeks after lesioning; however, the alternative grips were not replaced by the precision grip. These findings indicate that recovery includes both training-dependent and training-independent processes, and that the recovery of the precision grip is promoted by intensive post-lesion motor training.

3. Effects of rehabilitative training after spinal cord damage

Recovery of forelimb motor function was also investigated in rats whose spinal cord had been damaged. As in the case of cortically damaged rats, recovery of forelimb motor function was observed in rats that were trained on the affected forelimb after a lesion of the corticospinal tract at the cervical level (Girgis et al., 2007). However, the optimal timing for initiating rehabilitative training in the rats with spinal cord damage was inconsistent with that in cortically damaged rats; delayed rehabilitative training after spinal cord damage was as effective as early training in promoting recovery of forelimb movements (Krajacic et al., 2009). Furthermore, the recovery of cAMP signaling in the affected motor cortex was even better in those with delayed rehabilitative training (Krajacic et al., 2009). Thus, time-dependent effects of rehabilitative training may vary depending on the affected regions and pathways in the central nervous system. Further evidence from a monkey model of spinal cord damage is needed to establish a standard strategy for rehabilitative training in patients with such injuries because the relative contribution of the corticospinal tract to motor

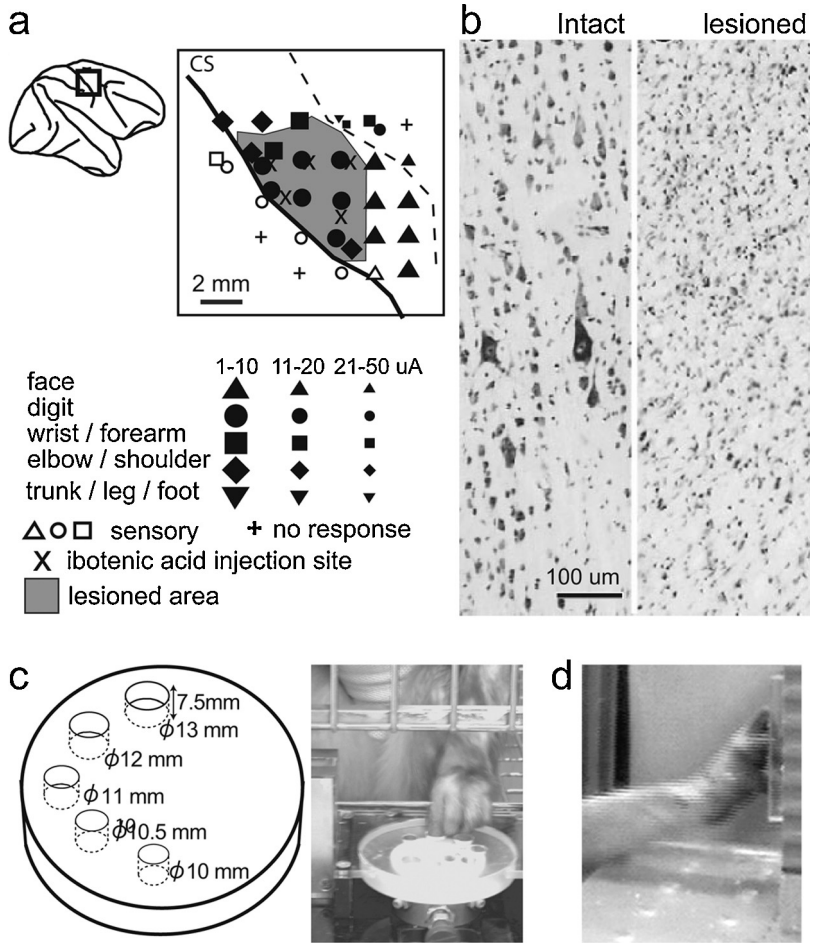

Fig. 1. Cortical lesions and behavioral testing in macaques. (a) Lesioned areas superimposed on intracortical microstimulation (ICMS) maps of primary motor cortex (M1). Movements elicited at threshold and sensory responses to light tactile stimuli are indicated by symbols. Some electrode penetration sites yielded no responses to ICMS at current strengths of up to 50 μA or to sensory stimulation. Hatched area indicates histologically confirmed lesion. Dotted line indicates the presumed border between M1 and the premotor cortex, which was determined by movement thresholds, sulcal landmarks, and cytoarchitecture as visualized by Nissl staining (Barbas and Pandya, 1987; Matelli et al., 1991; von Bonin and Bailey, 1947). CS, central sulcus. (b) Normal and ibotenic acid-lesioned areas of M1. Ibotenic acid injection resulted in loss of neurons and gliosis. (c and d) The two tasks used for both rehabilitative training and evaluation of manual skill in monkeys. The monkeys retrieve a small food pellet from cylindrical wells in the board task (c) and retrieve a small food morsel inserted into a vertical slit in the vertical-slit task. (d; Adapted from a previous report by Murata et al. (2008)).

behavior is suggested to differ between rodents and primates (Alstermark et al., 2004; Courtine et al., 2007; Isa et al., 2007; Kuypers, 1982; Lemon, 2008).

For understanding the time-dependent effects of rehabilitative training on functional compensation after spinal cord damage, our group conducted behavioral analyses and compared the recovery of dexterous hand movements between macaque monkeys in which hand motor training was initiated immediately after the corticospinal tract lesion (early-trained monkeys) and those in which training was initiated 1 month after the lesion (late-trained monkeys; Fig. 3a and b; Sugiyama et al., 2013). In this experiment, the ipsilateral lateral corticospinal tract (l-CST) was completely lesioned at the 4th or 5th cervical segment of the spinal cord (Fig. 3a), and procedures for the training and testing of dexterous hand movements were almost identical to those used for the M1-lesioned monkeys (Fig. 1c and d). In early-trained monkeys, the performance evaluated by the success rate in the vertical-slit task recovered to the level of intact monkeys during the first 1–2 months after lesioning (Fig. 3c). The hand movements of early-trained monkeys were similar to those observed before the lesion: the tip of the thumb approached the index finger smoothly during retrieval, and the food pellet was held by a precision grip (Fig. 3d). These results in the early-trained monkeys were consistent with our previous studies, in which daily training was initiated immediately after the l-CST lesion (Nishimura et al., 2007, 2009; Sasaki et al., 2004). In late-trained monkeys, the task success rate averaged about 30% even after 3 months of rehabilitative training (Fig. 3c) – a value significantly lower than either that in the early-trained monkeys or that before the lesion. In addition, the hand movements of the late-trained monkeys were different from those observed before the lesion even on trials with successful retrieval: the monkeys frequently retrieved the food pellet by raking it out of the slit with the index finger and then holding it between this finger and the proximal joint of the thumb (Fig. 3d). Thus, deficits in independent and coordinated movement between the index finger and thumb remained in the late-trained monkeys.

We also investigated the effects of rehabilitative training in cases the spinal cord lesion was incomplete and a portion, estimated at 15–30%, of the l-CST fibers remained intact. In this case, dexterous hand movements, including precision grip, was recovered to the level of intact monkeys by post-lesion training initiated 1 month after the lesion (unpublished observation). The result is consistent with a clinical observation of spinal cord injury patients, in which a portion of corticospinal tract fibers often remain intact and significant recovery of motor performance was observed with rehabilitative training initiated several months after the injury

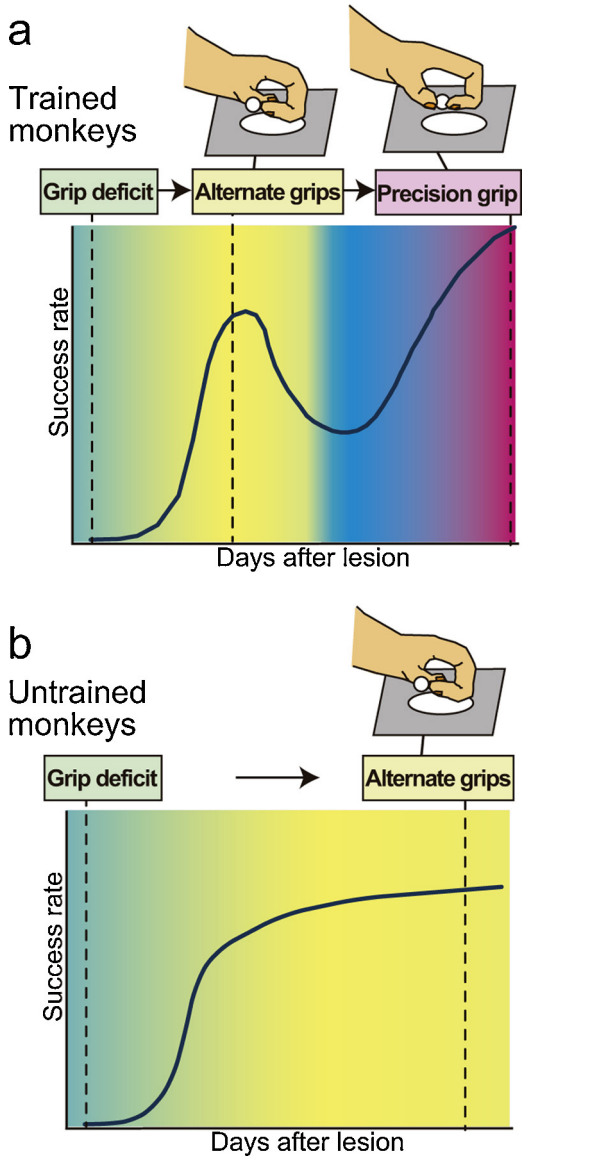

Fig. 2. Effect of training on recovery of dexterous hand movements. (a) Schematic illustration that shows the relationship between change in rate of success and change in grip form in monkeys that underwent intensive daily rehabilitative training after a focal lesion of the hand digit area of M1. Although 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 course of recovery, 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 alternative grip was gradually switched back to a precision grip. (b) In monkeys that did not undergo rehabilitative training, many alternative grips were observed; however, these grips were not replaced by the precision grip.
(Modified with permission from Murata et al. (2008)).

(Scivoletto et al., 2006), and thus suggests the importance of rehabilitative training, even when we miss the opportunity to initiate training early after the lesion. These results in a monkey model of corticospinal tract lesion suggest that early rehabilitative training after a spinal cord lesion positively influences subsequent functional recovery, especially when the l-CST is completely lesioned.

The results in the monkey model of l-CST lesion are apparently inconsistent with those in the rat model, which showed that delayed rehabilitative training was as effective as early training in promoting functional recovery of forelimb movements (Krajacic et al., 2009). This inconsistency may be ascribed to differences in the duration of the delay: whereas the delay between the early- and late-trained groups was only 8 days (4 d *vs.* 12 d) in the rat study, it was 1 month in the monkey study. The inconsistency may also indicate the importance of the monkey model in providing clinically applicable evidence for rehabilitation, because both the structure and function of the corticospinal tract differ between rodents and primates (see above).

4. Neural mechanisms involved in the functional recovery of hand movements induced by rehabilitative training

Many studies with both human patients and experimental animals have been conducted on the neuroplastic changes that are involved in functional recovery after the brain or spinal cord is damaged. For example, studies using spinal cord-lesioned monkeys showed that sprouting of midline-crossing axons of corticospinal tract occurs in the spinal cord rostral to the lesion, and the sprouting was associated with improvement in hand function and locomotion (Courtine et al., 2005; Rosenzweig et al., 2010). Another study in monkeys reported that sprouting of corticospinal axons and functional recovery after spinal cord lesion was enhanced by treatment with antibody against Nogo-A, a myelin-associated neurite outgrowth inhibitor (Freund et al., 2006). These studies have contributed to our understanding of neural mechanisms underlying the functional recovery after damage to the central nervous system.

The present review mainly focuses on studies of how rehabilitative training affects the plastic changes. The functional motor representation map was investigated in rats and squirrel monkeys, a New World monkey species, by using the ICMS technique after focal damage in the forelimb movement area of the motor cortex; the authors reported that the functional motor representation maps around the damage and remote cortical regions change with rehabilitative motor training (Barbay et al., 2013; Frost et al., 2003; Nudo et al., 1996; Ramanathan et al., 2006). Moreover, a previous study showed that the functional motor representation map around the damaged area in the motor cortex of squirrel monkeys is reorganized by early but not delayed rehabilitative training (Barbay et al., 2006). In this study, reorganization occurred such that the forelimb area reappeared in the region surrounding the damage; therefore, reorganization of the functional motor representation map is considered the neuronal basis of training-induced recovery of forelimb movements. Such a change in the functional map of the motor cortex also occurs during functional recovery after spinal cord damage (Girgis et al., 2007; Schmidlin et al., 2004). Thus, rehabilitative training after damage to the spinal cord, as well as after damage to the motor cortex, may reorganize the movement representation map in the motor cortex.

Changes in anatomical structure have also been reported as the basis of rehabilitative training-induced functional recovery (Carmichael et al., 2001; Dancause et al., 2005). In a study of cortically damaged rats, rehabilitative training of the affected forelimb was reported to enhance the dendritic complexity and length of layer 5 pyramidal cells in the motor cortex relative to those in rats without post-lesion training (Biernaskie and Corbett, 2001). Another study in rats with spinal cord lesions showed that rehabilitative motor training increases the number of collaterals of the corticospinal tract rostral to the damage in the spinal cord (van den Brand et al., 2012). These studies are examples of the effects of post-lesion motor training on neuronal structure.

As described above, our studies showed that the precision grip recovered in the macaque monkey with post-lesion training after a lesion of M1 or the corticospinal tract (Murata et al., 2008; Nishimura et al., 2007, 2009; Sasaki et al., 2004; Sugiyama et al., 2013). In either case, functional brain imaging studies using positron emission tomography (PET) demonstrated that the functional recovery was associated with changes in the activity of motor

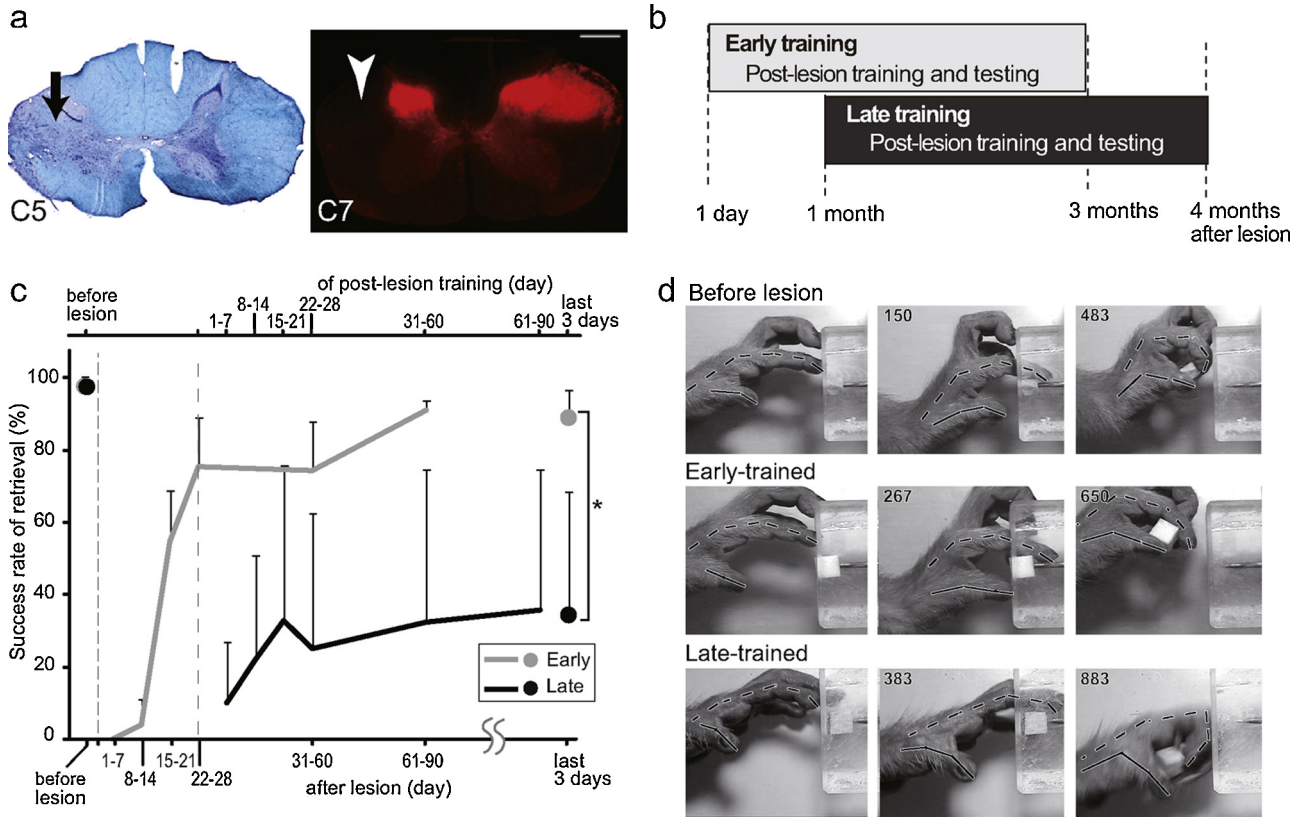

Fig. 3. Effect of training timing on functional recovery from a lesion of lateral corticospinal tract (l-CST). (a) Typical transverse spinal cord sections subjected to Klüver–Barrera staining in the 5th cervical segment of the spinal cord (C5) showing the location of a lesion (arrow), and 7th cervical segment (C7) from the same monkey subjected to immunofluorescence staining of the α-subunit of calcium/calmodulin-dependent protein kinase II, a marker of the corticospinal tract (Terashima et al., 1994). At the C7 segment, caudal to the lesion, the signal intensities in the left dorsolateral funiculus were markedly reduced (arrowhead). Scale bar = 1 mm. (b) Experimental design of the study. The early- and late-trained monkeys began training 1 day and 1 month, respectively, after a lesion of the lateral corticospinal tract. After 3 months of post-lesion training and testing, the extent of the lesion in the spinal cord was confirmed by histological analyses. (c) Temporal changes in success rates of retrieval in the vertical-slit task. The average values of the early- ($n = 3$) and late-trained ($n = 5$) monkeys are shown with standard deviations. The day of post-lesion training in the early-trained monkeys corresponds to the day after the lesion, whereas there was a gap of 1 month in the late-trained monkeys. The day of post-lesion training in the late-trained monkeys is indicated in the upper horizontal bar. All monkeys smoothly retrieved the piece of food from the vertical slit before the lesion, whereas impairment of hand function was observed immediately after the l-CST lesion. The average success rate of retrieval in the early-trained monkeys increased gradually after the lesion and reached the pre-lesion level during the post-lesion training period. The average success rate of retrieval in the late-trained monkeys after 3 months of post-lesion training was significantly lower than that in the early-trained monkeys ($^*P < 0.001$, Mann–Whitney U-test). (d) Sequence of photographs that show hand and digit movements before the lesion and after post-lesion training in early- and late-trained monkeys performing the vertical-slit task. The joints and tips of the thumb and index finger are linked by solid and dotted lines, respectively. Each photograph from left to right shows the moment of contact of the index finger tip with the aperture of the slit, the moment of contact of the index finger tip with the food morsel, and the moment of removal of the digits from the slit, respectively. In the early-trained monkey after post-lesion training, the tip of the thumb smoothly approached the index finger during retrieval, and the food pellet was held between the pads of the index finger and thumb, similar to the movements observed before the lesion. In contrast, the late-trained money could approach the food pellet with its index finger but then could not bring the thumb near the index finger. The time intervals (ms) relative to the leftmost image are indicated at the top of each image.
(Modified with permission from Sugiyama et al. (2013)).

cortical areas (Murata et al., 2011; Nishimura et al., 2007). Pharmacological inactivation of cortical areas that showed increased brain activity during the recovery phase resulted in more severe impairment of hand movements than inactivation of the same area before the lesion, indicating that the changes in activity are involved in the recovery of hand movements. We also investigated the gene expression of growth-associated protein-43 (GAP-43), a plasticity-related molecule whose expression is related to axonal sprouting and the structural alteration of synapses (Benowitz and Routtenberg, 1987, 1997; Denny, 2006). Gene expression of GAP-43 increased in the excitatory neurons of the ventral premotor area during the recovery phase after lesion of either M1 (Murata et al., 2011) or the corticospinal tract (Higo et al., 2009), suggesting that remodeling of axon terminals may occur in the excitatory projection neurons of the ventral premotor cortex. Preliminary observations indicated that the gene expression of GAP-43 was higher in monkeys given rehabilitation training than in untrained monkeys, suggesting that GAP-43 expression may be induced by rehabilitative motor training. In a previous study, we showed that GAP-43 expression is regulated in an activity-dependent manner (Higo et al., 2000). Therefore, this gene may have a key role in the activity-dependent neuroplastic changes that underlie the functional recovery induced by rehabilitative training.

5. Conclusions

In several recent studies, the effects of rehabilitative training have been reported and major contributions have been made not only by clinical research on human patients but also by basic research on rodents and monkeys. Experimental studies on rats have the advantage that large numbers of subjects are available, whereas studies on monkeys are also important because their brain and body structures are similar to those of humans. Dexterous hand movements, whose impairment is a major issue in patients whose central nervous system has been injured because such movements are essential for the quality of human life, are as developed in

some monkey species as in humans. Common neural mechanisms may underlie the hand movements of these species; *e.g.*, we have recently found a gene that is expressed in the corticospinal neurons of highly dexterous monkey species and humans but not in those of less dexterous monkey species and rodents (Higo et al., 2010; Yamamoto et al., 2013).

On the whole, recent studies of both rodents and monkeys have greatly contributed to our understanding of the effects of certain rehabilitative procedures on functional recovery after brain or spinal cord damage. However, our knowledge concerning the neural basis of training-induced functional recovery remains fragmentary. Further studies with experimental animals are needed to understand all of the processes that underlie the functional recovery induced by rehabilitative training, including changes in brain activity, neural circuits, and gene expression.

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