Although brain damage causes functional impairment, it is often followed by partial or total recovery of function. Recovery is believed to occur primarily because of brain plasticity. Both human and animal studies have significantly contributed to uncovering the neuronal basis of plasticity. Recent advances in brain imaging technology have enabled the investigation of plastic changes in living human brains. In addition, animal experiments have revealed detailed changes at the neural and genetic levels. In this review, plasticity in motor-related areas of the cerebral cortex, which is one of the most well-studied areas of the neocortex in terms of plasticity, is reviewed. In addition, the potential of technological interventions to enhance plasticity and promote functional recovery following brain damage is discussed. Novel neurorehabilitation technologies are expected to be established based on the emerging research on plasticity from the last several decades.

Keywords: brain damage, functional recovery, motor cortex, plasticity, rehabilitation

1. Introduction

The ability of neurons to change their structure and function in response to environmental alterations in the mature brain is called neural plasticity. It has been less than a century since the ability of neuronal structures to undergo persistent changes was clearly identified for the first time [1–6]. Subsequently, numerous studies have reported evidence of the brain’s capacity to change its structure and function. Plasticity is widely accepted as the foundation of learning and memory in the intact brain and is also believed to be involved in functional recovery following brain damage caused by stroke and other disorders [7–12], that is a typical example of hyper-adaptability, which is dynamic reconstruction of the neural circuits that underlies compensation for neural function loss. Understanding the mechanisms of plasticity that emerge in the process of functional recovery following brain damage will lead to the development of innovative technologies, including robot-assisted rehabilitation technologies that promote brain function recovery. This study focused on plasticity in the motor cortex, which plays an important role in motor learning and motor function recovery.

The motor cortex is one of the most well-studied brain areas in terms of plasticity, partially because of its unique structural characteristics. It is organized into distinct areas based on structural and functional criteria, such as the primary motor cortex (M1), supplementary motor cortex, and premotor cortex, and the areas are hierarchically arranged to coordinate movements [13–15]. M1 is responsible for most of the motor output from the neocortex and has a topographically organized map of body parts in which regions responsible for movement are arranged on the surface of the cortex [16, 17]. Topographic body maps are also observed in the supplementary motor cortex and premotor cortex, although that in the latter is unclear and incomplete [16, 18]. Several lines of evidence have shown that the topographic body map of the motor cortex can change under various conditions. Plasticity in the motor cortex has also become well known owing to its advantages in analyzing correlations with behavior. Changes in the motor cortex associated with behavioral changes during motor learning and recovery are easier to study than changes in the cortical area associated with changes in other functions, such as sensory and cognitive functions.

Although plastic changes in the motor cortex have been identified in the human brain owing to recent advances in brain imaging technology, animal experiments have revealed more detailed changes at the neural and genetic levels. Moreover, because animals can be experimentally manipulated, animal experiments can verify the causality between plastic changes in the cortical area and behavioral changes. In this review, plastic changes in the motor cortex obtained from both human and animal studies are outlined.

2. Functional Changes

2.1. Motor Learning

Neural plasticity underlies functional recovery following brain damage; however, the mechanism is believed to have been acquired during the evolutionary process as a
2.2. Functional Recovery

Functional recovery occurs with appropriate rehabilitative training following brain damage [28,29]. However, it has been suggested that, with some exceptions, lost neuronal cells do not regenerate in the mature brain [30–33]. Moreover, reactive gliosis and glial scar formation in the lesion core prevent neurons from regenerating and elongating their neurites [34–36]. Therefore, functional compensation is believed to occur in undamaged brain regions as the basis for functional recovery. Because the process of functional recovery following brain damage involves more dynamic changes than motor learning, considerable evidence has been accumulated on plasticity during recovery. The neural mechanisms underlying functional recovery have been investigated in human patients with brain damage, whereas major contributions have also been made in experimental animal studies in which brain damage is artificially induced [37–42].

A change in the topographic body map was reported in a study that induced local damage in the hand representation in M1 of squirrel monkeys [42]. In this study, new regions related to hand and wrist movements appeared in the body region originally responsible for movements of the elbow and shoulder when rehabilitative motor training using a grasping task was performed after damage, whereas such changes did not occur without rehabilitation training. These results suggest that changes in the topographic body map of the motor cortex are the basis of motor function recovery during rehabilitation training. Functional recovery mechanisms after M1 damage have also been studied in macaque monkeys that have brains with a highly folded cortex similar to that of humans [43–47]. Before the damage, the monkeys were able to grasp small objects using dexterous movements with the tips of their thumb and index fingers (precision grip), whereas the monkeys were severely paralyzed after damage to the hand representation of M1 [29]. Monkeys who underwent rehabilitation training after the damage showed recovery of dexterous hand movements, including precision grip [29]. Because M1 is considered an essential brain region for precision grip [40], large-scale plastic changes are assumed to occur to compensate for the function of M1. Functional brain imaging revealed changes in brain activity during grasping in M1 around the damaged area and in the ventral premotor cortex (PMv), where motor plans for hand movements are generated [17]. Additional experiments have shown that when activity in these areas is suppressed by muscimol, a GABA_A receptor agonist, the execution of precision grip is impaired, suggesting that changes in motor cortex activity are essential for functional recovery of precision grip after M1 damage [17].

To mimic the pathophysiology of stroke in patients using an animal model, artificial stroke was induced in the internal capsule, where the descending motor tracts were located [48–50] (Fig. 1, upper panels) [51–54]. In comparison with models involving M1 damage, animal models contribute to the exploration of key factors that are essential to motor recovery in patients because the severity and outcome of motor dysfunctions are based on damage to the internal capsule [48–50]. A study using the macaque model of internal capsular infarcts reported compensatory changes in motor cortical activity, including increased activity of the PMs during voluntary movements after motor recovery (Fig. 1, middle panels) [55]. Similar changes in motor cortical activity were also reported in patients who had functionally recovered from strokes [56, 57]. In both the macaque model of internal capsular infarcts and stroke patients, the cortex contralateral to the stroke played a greater role in recovery when damage by stroke was more severe (Fig. 1, lower panels) [58–66].

Functional changes in the motor cortex have also been shown to occur after damage to the spinal cord, which is the output pathway for motor information rather than the motor cortex itself. In macaque monkeys, severing the corticospinal tract, the main motor output pathway from the motor cortex to the spinal cord, resulted in tempo-
Higo, N.

Before damage After recovery
Fig. 1. (Upper panels) MRI showing the location of stroke in the left internal capsule (coronal, axial, and sagittal images). Scale bars = 10 mm. Reproduced from Fig. 1 of the study by Murata and Higo [54]. (Middle panels) Brain activation during hand movements before damage (left) and after motor recovery from stroke (right). Before damage, activation was observed in the hand area of M1. After motor recovery, increased activation was observed in PMv. (Lower panels) The contralateral cortex to the stroke plays a greater role in recovery when damages are more severe. Reproduced from Fig. 2 and 4 of the study by Kato et al. [55].

3. Structural and Molecular Changes

Because neural anatomical structures underlie brain function, functional changes in the brain involve structural changes in neuronal cells, such as axons, dendrites, and synapse formation [69–71]. Although recent advances in brain imaging technology have enabled to investigate not only functional but also structural changes in living human brains [72–74], the structural mechanisms underlying functional changes in the motor cortex have been more thoroughly investigated in experimental animals, owing to the possibility of genetic modifications and histological analysis. Recent advances in optogenetic research have revealed changes at the cellular level during motor skill learning [75, 76]. Observations of synaptic dynamics during motor skill learning in rodents have shown that postsynaptic dendritic spines were formed and immobilized on specific output pyramidal neurons [76]. The molecular mechanisms that caused such cellular changes have also been elucidated, and comprehensive gene expression analysis in rodents has revealed the expression of genes related to synaptic plasticity, synaptogenesis, and cytoskeletal dynamics after motor learning [77]. Optogenetic studies have also shown an increase in α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic-acid (AMPA)-type glutamate receptors in postsynaptic dendritic spines following motor learning [78]. Because motor learning is impaired in rodents lacking the N-methyl-D-aspartate (NMDA) receptor in M1, this receptor may also be involved in motor learning [79].

There are many genes whose expression is known to change following brain damage. Transcriptome analyses, which catalogue all transcripts expressed within a sampled tissue, have contributed to the identification of gene expression changes [80–85]. Most upregulated genes immediately following brain damage may be related to the progression of brain damage, such as neuronal death, inflammation, and subsequent atrophy [86–90]. In addition, there are genes whose expression is suggested to be involved in functional recovery that occurs days to months following brain damage. The expression change occurs not only in genes that are involved in the function and structure of neurons, but also in those involved in the function and structure of glial cells, such as microglia and astrocytes, which also have roles in neural plasticity [91–101]. In a study using a rodent model of brain damage, genes involved in structural changes of neurons were upregulated in the neighboring brain regions of the damaged motor cortex [102]. For example, the expression of growth-associated protein-43 (GAP-43), which is believed to be involved in axonal sprouting and synaptic remodeling in neurons [103–105], increases to induce structural changes in projections originating in the neighboring brain regions to damage [69]. In macaque monkeys, such changes in projection have been reported not only in the regions neighboring the damage but also in other motor areas involved in functional compensation; formation of new projections originating in the PMv was observed after artificial damage to M1 [106, 107]. The expression of plasticity-related genes, such as GAP-43, increased in motor cortical areas where structural changes were reported after M1 damage in macaque monkeys [108]. The increased expression was transient during the period when functional recovery of forelimb movements was most
marked (1–1.5 months after damage), and most prominent in the large excitatory neurons in layer V, where descending projections from the PMVs originated. Therefore, this expression may be involved in the rewiring of connections from the PMVs to subcortical structures [107].

Experiments in spinal cord lesioned macaque monkeys also suggested that structural changes in the corticospinal tract originating in the motor cortex occurred with functional recovery after the lesion [109, 110]. Similar to results obtained in the brain damage model, the gene expression of GAP-43 in the motor cortex of macaque monkeys increased in several motor-related areas during recovery from spinal cord lesions [111]. Regulation of expression was observed in neurons in layer III, which are responsible for projections between different cortical areas, as well as those in layer V cells, which are responsible for subcortical projections, including the corticospinal tract, suggesting that changes occurred in various projection pathways in the motor cortex during recovery. Microarray analysis in macaque monkeys after the spinal lesion showed that a large number of genes exhibited altered expression levels in the contralesional M1, which directly sends efferent projections to the lesioned hemicord during the early stage (approximately two weeks after the lesion) when motor recovery is not evident [112]. Gene ontology and network analyses indicated that these changes in gene expression were mainly involved in the degenerative changes of neurons. In contrast, orchestrated gene expression changes were observed when recovery of motor function was attained three months after the lesion. A marked change in gene expression was observed in the premotor areas, and many of these genes were involved in plastic changes in neuronal structures. These area-specific and time-dependent changes in gene expression may underlie the molecular mechanisms underlying functional recovery [112]. Notably, the genes differentially regulated in the spinal cord-lesioned macaque monkeys were abundantly expressed in M1 of the intact monkeys and those upregulated in the premotor areas during recovery after the lesion. The SPP1 gene, also known as osteopontin, is mainly expressed in neurons projecting to the corticospinal tract in M1 [113, 114] and is an example of this pattern of expression change [112]. M1 is the main source of motor output in intact animals, however it is possible that the premotor areas become directly involved in motor output after damage to the central nervous system [17, 68, 115] by strengthening the descending projections from the premotor areas [116]. The shift in the expression areas of genes may be the molecular basis underlying the dynamic reorganization of cortical areas, which involves the reestablishment of motor output projections during the functional recovery of voluntary movements after damage.

4. Strategies to Promote Functional Recovery

4.1. Rehabilitative Training

Based on clinical experience, it is believed that rehabilitative training promotes functional recovery following brain damage. Because it is difficult to control patients’ daily lives or establish a control group in which no rehabilitation training is carried out, studies using animal models have contributed to elucidating the effects of rehabilitation training on behavioral recovery [28]. As described above, recovery of dexterous hand movements was induced by intensive post-lesion rehabilitative training using the affected hand in a macaque model of M1 damage [29]. However, those who did not undergo rehabilitation training tended to fixate on compensatory grasping using coarse movements without independent control of the fingers, indicating that recovery of dexterous hand movements after motor cortex damage was induced by intensive rehabilitative training [29]. Moreover, rats that had undergone motor training in object retrieval using the affected forelimb after sensorimotor cortex damage showed recovery of forelimb movements, however such recovery was not observed with full-body motion training using a running wheel [117]. This result indicated that rehabilitative training, in which the affected body part was specifically involved, was more effective than training in which several body parts were involved. In rats that underwent motor training using the upper limb after motor cortex damage, greater dendritic arborizations in the contralateral motor cortex were observed compared with those who did not undergo rehabilitative training [118]. This is an example of how rehabilitative training affects the plastic changes in the motor cortex.

Because rehabilitative training is the standard of care after brain damage, the development of a novel rehabilit-
tation approach to improve the effectiveness of rehabilitation is one of the most important goals of research in this field. To maximize the effect of rehabilitative training on functional recovery, it is particularly important to determine the ideal timing for training onset following brain damage occurs. In a rat model of brain damage, the recovery of forelimb movements was compared among subjects who initiated motor training 5, 14, or 30 d after the damage [119]. The study showed that the level of recovery was highest in the group that began motor training five days after lesioning, the earliest time point [119]. Another study using macaque monkeys also indicated that rehabilitative training at an earlier time point after damage was more effective for functional recovery [120]. Movements immediately following brain damage have been reported to intensify the initial damage because glutamate release occurs and induces a neurotoxic effect [121–124]. Therefore, motor training during the early period after damage may be more effective because the increase in brain plasticity during this period induces a larger scale of functional reorganization of undamaged brain regions [102], despite intensifying the initial damage.

Another direction of rehabilitative training is robot-assisted rehabilitation technology. Currently, the effects of robot-assisted rehabilitation on the recovery of motor function in stroke patients have been shown to be comparable to, but not significantly superior to, the effects of conventional rehabilitation assisted by medical personnel such as physical and occupational therapists [125]. Therefore, robot-assisted rehabilitation technologies may be effective in compensating for the shortage of therapists, even though the shortage of skilled therapists may become an issue in the future. In addition, using computer technology to intervene at the right time, the effects of robot-assisted rehabilitation can be expected to exceed those of conventional therapies. Brain-machine interfaces (BMIs) translate neuronal signals into computerized commands, which can then be used to stimulate the paralyzed limbs of patients with brain damage at the right time to establish a contingent link between them [126, 127]. Although further research is required, BMI-based control of robotic devices is a promising technology for rehabilitation that maximizes plasticity for functional recovery.

4.2. Medication

As described above, structural changes in neurons and changes in the expression of genes responsible for neuronal structural changes occur to compensate for the functions of lost neuronal tissue. Acceleration of these changes promotes functional recovery following brain damage. Medication may be useful for accelerating these changes. A study using a rat model of brain damage showed that motor performance was strongly improved when rehabilitative training using the affected forelimb was combined with treatment with the anti-inflammatory drug minocycline, which inhibits microglial activation [128]. Microglial inhibition is believed to have positive effects on functional recovery because microglia cause neuronal degeneration. Other factors are known to inhibit plastic changes in neurons after damage to the central nervous system. Nogo-A, a myelin-associated inhibitory factor [129], and chondroitin sulfate proteoglycans within the extracellular matrix of glial scar [130–132] inhibit axonal regeneration and sprouting. In animal models, medications to inactivate these proteins successfully achieve functional recovery after damage to the central nervous system [133, 134].

Medications aimed at directly accelerating neuroplastic changes have also been suggested. A small compound, edenoperpic maleate, was reported to facilitate experience-driven synaptic glutamate AMPA receptor delivery in cortical neurons, resulting in the acceleration of motor function recovery in both mice and monkeys following brain damage [135]. Subcortical input has also been reported to be a factor in inducing plastic changes in the motor cortex. Studies in rodents have shown that input from acetylcholinergic neurons in the basal forebrain to the motor cortex is essential for plastic changes in the motor cortex during both motor learning and recovery of motor function following brain damage [136–138]. Therefore, potentiation of acetylcholine release by medication may promote the recovery of motor function following brain damage.

4.3. Neuromodulation

Neuromodulation using electrical stimulation has attracted attention for the promotion of functional recovery following brain damage. Typical examples of neuromodulation using electrical stimulation include TMS and transcranial direct current stimulation (tDCS). TMS changes the magnetic field to cause electric current in a specific area of the brain through electromagnetic induction. tDCS is a technique in which a direct current (DC) of approximately 1 mA is applied to the scalp. Although tDCS does not provide localized stimulation as TMS does, it is safer than TMS. Moreover, the equipment is relatively inexpensive and can be used for rehabilitative motor training. Studies on stroke patients have reported that combined anodal stimulation of the motor cortex of the damaged hemisphere and cathodal stimulation of the contralateral intact hemisphere applied by tDCS promote functional recovery of the upper limbs [139–141]. On the contrary, stimulation was reported to have limited efficacy in stroke patients with severe upper limb paralysis [142], indicating the scope for technical improvements. To establish a more effective neuromodulation technology, it is essential to uncover the effects of neuromodulation on the cortical areas. Studies using animal models of brain damage have contributed to this research.

Anodal stimulation is believed to promote activity in the stimulated brain area, whereas cathodal stimulation is believed to suppress activity in the stimulated brain area [143]. In stroke patients, the activity of descending pathways originating from the motor cortex is decreased in the damaged hemisphere and increased in the contralat-
eral intact hemisphere owing to the reduction of inter-hemispheric inhibition [144, 145]. Therefore, anodal stimulation of the damaged hemisphere and cathodal stimulation of the contralateral intact hemisphere are believed to bring brain activity closer to that in the normal intact brain. However, because functional reorganization of the damaged brain and changes in activity are essential for functional recovery, as described above, stimulation that brings the brain closer to normal activity may not always promote functional recovery. Further understanding of the plastic changes underlying functional recovery is required to tailor the neuromodulation to the patient’s condition. It has also been suggested that anodal stimulation of the motor cortex can induce LTP, and a study of healthy human subjects showed that stimulation can alter connections within the motor cortex [146]. As described above, the topographic body map reorganizes during the recovery from rehabilitative training after motor cortex damage [42], and anodal stimulation may therefore induce this reorganization by changing connections in the motor cortex. In fact, a study on monkeys reported that the combination of electrical stimulation and rehabilitative motor training of the upper limb using grasping movements promoted changes in the topographic body map [147].

The molecular mechanisms underlying plastic neural changes induced by neuromodulation have also been reported. Magnetic resonance spectroscopy studies suggested that anodal tDCS decreased the concentration of the inhibitory neurotransmitter GABA, whereas cathodal tDCS decreased the concentration of both GABA and glutamate, an excitatory neurotransmitter [148]. Studies using slices of the mouse motor cortex showed that LTP induced by anodal stimulation involved NMDA receptors and the neurotrophic factor brain-derived neurotrophic factor (BDNF) and its receptor TrkB [149]. A study using a rat model of brain damage showed that anodal tDCS for five consecutive days increased the expression of GAP-43, which is believed to be involved in structural changes of neurons during functional recovery, as described above. Because GAP-43 is expressed in an activity-dependent manner [150], increased neural activity by stimulation may induce GAP-43 expression.

5. Species Differences

As mentioned above, studies in both animals and humans have contributed to our knowledge of the plasticity of the motor cortex. Notably, there are species differences, and observations using animal models are not necessarily applicable to humans. Rodents are the mammals most commonly used for experimental studies because they have the advantage of being bred to reduce biological variation, while being easy to breed and maintain in laboratory conditions. Moreover, genetic manipulation technologies are easily applicable to rodent models, particularly in mice. Therefore, experimental studies in rodents have contributed to elucidating the structural and gene expression changes during functional recovery following brain damage. The neuronal structure of rodents is highly similar to that of humans compared to that of non-mammalian experimental animals such as zebrafish, fruit flies, and nematodes. However, the neuronal structures in certain brain areas differ between rodents and humans. This differentiation can lead to a gap between basic studies in rodents and clinical studies in humans.

In addition to rodents, monkeys are important experimental animals because of their close similarity to humans [151]. Among nonhuman primates, macaque monkey models are commonly used in neuroscience. Their brain structures and functions closely resemble those of humans, including those involved in motor function. For example, the motor cortices of primates, but not rodents, are organized into distinct areas based on structural and functional criteria, and these areas are hierarchically arranged to coordinate fine movements of the digits and limbs [13–15]. It is widely accepted that macaque monkeys have musculoskeletal structures that are more similar to humans than rodents. For example, the musculoskeletal system of the forelimb of macaque monkeys as well as the cortical projection to the spinal cord are similar to humans, and dexterous hand function is as highly developed as it is in humans [44, 152, 153]. The gene expression profile in the brains of macaque monkeys is closer to that in humans than in rodents [154, 155].

Macaque monkeys are also more similar to humans than rodents in terms of brain structure and cellular changes related to functional recovery following brain damage. For example, the pattern of myelination in the macaque brain is more similar to that in the human brain than that in the rodent brain [156]. Because myelin debris, which is produced after stroke, is toxic to neurons [157], similarity in myelination is critical to investigate functional recovery mechanisms following brain damage in humans [152]. Moreover, the time course of the proliferation of microglia as well as their function following brain damage is believed to be different between primates, including both macaques and humans, and rodents [158–163]. Although a study using a rat model of brain damage suggested that microglial inhibition is believed to have positive effects on functional recovery, as described above [128], further studies using the macaque model of brain damage are likely to facilitate translational outcomes considering the similarity in the characteristics of microglia.

However, species differences, even those between macaques and humans, should be acknowledged when interpreting the results of studies using animal models. For example, language function is primitive in macaque monkeys, and the degree of hemispheric lateralization and handedness varies among species [164, 165]. Although gene expression profiles are similar between macaques and humans, some of these expressions are specific to humans [166–168]. Therefore, further validation and careful interpretation are required to develop innovative technologies based on observations obtained from animal models.
6. Conclusion

Studies in humans and animals have provided insights into plastic changes in the motor cortex. Currently, very few rehabilitation technologies can assist functional restoration in patients with brain damage based on the neural plasticity mechanism. Therefore, novel neurorehabilitation technologies based on functional recovery mechanisms are expected to be developed.

The temporal cortex and other association areas are known to store long-term association memory [169, 170]. The expression of genes involved in neuroplasticity in the adult brain is higher in the association area than in the motor area, and this scheme has also been identified in the sensory relay nuclei [171–174]. Future progress in this field will lead to the establishment of techniques that promote the recovery of motor and nonmotor functions, including cognitive and sensory functions.

Acknowledgments

This work was supported by KAKENHI (Grant Nos. 20H04061 and 20H04236) from the Japan Society for the Promotion of Science, a Grant-in-Aid for Scientific Research on Innovative Areas, “Hyper-adaptability for overcoming body-brain dysfunction: Integrated empirical and system theoretical approaches” (Grant No. 20H05490) from the Ministry of Education, Culture, Science, Technology, and Japan.

References:


R. J. Nudo, R. M. Wise et al., “Neural substrates for the effects of 

B. Alstermark, J. Ogawa et al., “Lack of monosynaptic corticomus-
toneuron reflexes in rats: Disynaptic EPSPs mediated via retico-
lospinal neurons and polysynaptic EPSPs via segmental interneu-

G. Courtime, M. B. Bunge et al., “Can experiments in nonhuman 

T. Isa, Y. Ohki et al., “Direct and indirect cortico-motorneuronal 

H. G. J. M. Kuypers, “A new look at the organization of the motor 

R. N. Lemon, “Descending pathways in motor control,” Annual Re-

C. Rosso, O. Colliot et al., “Focal Malonate Injection into the In-
ternal Capsule of Rats as a Model of Lacunar Stroke,” Front. Neu-
rosci., Vol.9, Article No.1072, 2018.

C.-W. Han, K.-H. Lee et al., “An Experimental Infarct Targeting the Internal 
Cortex as a Model of Lacunar Stroke,” Front. Neu-
rosci., Vol.9, Article No.1072, 2018.

S. Bajaj, S. N. Housley et al., “Dominance of the Unaffected Hemi-

S. Puentes, T. Kaido et al., “Internal capsule stroke in the common 

Y. Murata and N. Higo, “Development and characterization of 
a macaque model of focal internal capsular infarcts,” PloS One, Vol.11, No.5, Article No.e0154752, 2016.

J. Kato, T. Yamada et al., “Functional near-infrared-spectroscopy-
based measurement of changes in cortical activity in macaques 

U. Horn, S. Roschka et al., “Increased ventral premotor cortex re-
cruitment after arm training in an fMRI study with subacute stroke 

I. Loubinoux, S. Dechaumont-Palacin et al., “Prognostic value of 
the contralesional motor cortex for motor recovery in the early days after stroke assessed 

J. D. Schaechter and K. L. Perdue, “Enhanced cortical activation 

B. Touvykine, B. K. Mansoori et al., “The Effect of Lesion Size on the Organization of the Ipsilesional and Contralesional Motor Cor-

S. Sasaki, T. Isa et al., “Dexterous finger movements in primate 
without monosynaptic corticomotorneuronal excitation,” J. Neuro-

Y. Nishimura, H. Oono et al., “Time-dependent central compen-
satory mechanisms of finger dexterity after spinal cord injury,” Sci-

S. T. Carmichael, L. Wei et al., “New patterns of intracortical pro-

B. B. Johansson and B.-L. Ohlsson, “Environment, social interac-
tion, and physical activity as determinants of functional outcome af-

B. B. Johansson and B.-L. Ohlsson, “Environment influences func-

R. Lindenberg, L. L. Zhu et al., “Predicting functional motor potential 
in chronic stroke patients using diffusion tensor imaging,” Hum. 

S.-H. Jang, “A review of diffusion tensor imaging studies on mo-
tor recovery mechanisms in stroke patients,” NeuroRehabilitation, 
Vol.28, No.4, pp. 345-352, 2011.

P. R. W. Arachchige, S. Karunarathna et al., “Changes in brain mor-
phometry after motor rehabilitation in chronic stroke,” Somatosens. 

K. Chen, Y. Zheng et al., “Exercise training improves motor skill 


V. C. K. Cheung, C. Deboer et al., “Gene expression changes in the 

R. H. Roth, R. H. Cudmore et al., “Cortical Synaptic AMPA Re-

M. T. Hasan, S. Hernández-González et al., “Role of motor cortex 
NMDA receptors in learning-dependent synaptic plasticity of be-

S. Li, J. J. Overman et al., “An age-related sprouting transcriptome 
provides molecular control of axonal sprouting after stroke,” Nature 

J. Kaiser, M. Marbach et al., “The Spinal Transcriptome After Cor-
tical Stroke: In Search of Molecular Factors Regulating Sponta-

M. Ito, M. Aswendt et al., “RNA-Sequencing Analysis Revealed a 
Distinct Motor Cortex Transcriptome in Spontaneously Recovered 

J.-B. Kim, C.-S. Piao et al., “Delayed genomic responses to tran-
sient middle cerebral artery occlusion in the rat,” J. of Neurochem-

A. Rönning, P. Dahlqvist et al., “Gene expression profiling of the 
rat hippocampus one month after focal cerebral ischemia followed 

K. Munutani, S. Sonoda et al., “Alteration of protein expression pro-
file following voluntary exercise in the perilesional cortex of rats 
with focal cerebral infarction,” Brain Research, Vol.1416, pp. 61-
68, 2011.

J.-H. Yi, S.-W. Park et al., “The role of transcription factors mediat-
ing post-ischemic cerebral inflammation and brain damage,” Neu-

M. Ahmad, N. J. Dar et al., “Inflammation in ischemic stroke: 
Mechanisms, consequences and possible drug targets,” CNS & 
Neurological Disorders – Drug Targets, Vol.13, No.8, pp. 1378-
1396, 2014.

Z. Zheng, J. E. Lee et al., “Stroke: Molecular mechanisms and po-

G. Ford, Z. Xu et al., “Expression analysis systematic explorer (EASE) analysis reveals differential gene expression in permanent and 

J. J. Velier, J. A. Ellison et al., “Caspase-8 and caspase-3 are 
expressed by different populations of cortical neurons undergoing de-

J.-C. Delpech, C. Madoré et al., “Microglia in neuronal plasticity: 


