REVIEW ARTICLE

Mechanisms Underlying Functional Recovery Following Stroke

Robert G. Lee and Paul van Donkelaar

ABSTRACT: This article reviews recent evidence from animal experiments indicating that there is considerable potential for reorganization of representations and functions in sensory and motor cortex following localized lesions or various manipulations of peripheral target structures. Three major mechanisms for this plastic reorganization are considered: unmasking of existing but functionally inactive pathways, sprouting of fibers from surviving neurons and formation of new synapses, and redundancy of CNS circuitry allowing alternative pathways to take over functions. Studies using positron emission tomography or transcranial magnetic stimulation suggest that similar forms of neuroplasticity may occur in the human brain and could contribute to functional recovery following stroke. The potential therapeutic implications are discussed.

RÉSUMÉ: Récupération fonctionnelle après un accident vasculaire cérébral: mécanismes sous-jacents. Nous revoyons les données récentes de l'expérimentation animale indiquant qu'il existe un potentiel considérable de réorganisation des représentations et des fonctions dans le cortex sensitif et moteur suite à des lésions localisées ou à des manipulations variées de structures cibles périphériques. Nous considérons trois mécanismes majeurs de cette réorganisation plastique: la manifestation de voies existantes mais fonctionnellement inactives, le bourgeonnement de fibres à partir de neurones survivants et la formation de nouvelles synapses, et la redondance de circuits du SNC permettant à des voies alternatives de prendre la relève. Des études faites à l'aide de la tomographie par émission de positrons ou de stimulation magnétique transcrânienne suggèrent que des formes analogues de neuroplasticité pourraient exister dans le cerveau humain et pourraient contribuer à la récupération fonctionnelle suite à un accident vasculaire cérébral. Nous discutons des implications thérapeutiques potentielles.

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Until recently it has been generally believed that once an area of brain has been infarcted or otherwise damaged that there is little or no potential for functionally effective regeneration or replacement of lost neurons. Despite this limitation the majority of patients who survive an acute stroke do show some evidence of improvement over time, and in some cases there may be quite remarkable recovery of function from what initially appeared to be an incapacitating hemiplegia. Early recovery during the first few days following a stroke is likely due to factors such as resorption of edema and necrotic tissue, or opening of collateral channels for circulation to the damaged region. But late recovery – after the first 3 to 4 weeks – must be due to other mechanisms which fall within the general realm of neuroplasticity. This implies that some areas of the brain may be able to take on new functions which were previously performed by the damaged region. In some situations functions may be transferred to immediately adjacent functionally related areas of cerebral cortex. In other cases transfer of function may occur to more remote sites in the same hemisphere, or perhaps even to the undamaged contralateral hemisphere. This raises the intriguing possibility that uncrossed motor pathways may play some role in functional recovery following damage to one cerebral hemisphere.

Three main mechanisms for these plastic changes have been considered:[1] **unmasking** which implies opening up, possibly by release from tonic inhibition, of pathways which exist anatomically but which have been functionally inactive, **sprouting** of fibers from surviving neurons with formation of new synapses, and **redundancy** in CNS circuitry, a concept which suggests that there are multiple parallel pathways subserving similar functions and that an alternative pathway may take over when another has been damaged.

In this review we shall examine the evidence that these mechanisms are responsible for functional reorganization in the central nervous system following localized damage or other perturbations. We will consider several studies on experimental animals where microelectrode mapping techniques have been used to demonstrate reorganization of cortical sensory or motor areas. We will also review observations from studies using functional imaging techniques or transcranial magnetic stimulation on human patients who have suffered strokes. Although the focus will be on functional recovery following stroke, the general principles which will be discussed likely apply to recovery following brain injury due to a variety of different insults. We will

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concentrate primarily on recovery of motor function, but it should be recognized that recovery following stroke involves many other functions including speech, cognition, and sensation.

Reorganization of Cortical Representations

In the past it has been assumed that the patterns of connectivity within the mature brain are relatively static. Following a period of great malleability during development, the cortical microstructure was thought to subsequently remain unchanged throughout the lifespan of the animal. More recently, however, an increasing body of evidence has demonstrated that cortical plasticity is possible in the adult CNS. In particular, a variety of manipulations have been shown to induce relatively large scale changes in the somatotopic representations within a number of different areas of the brain, including the sensory and motor cortices. The mechanisms which mediate these plastic changes may provide some insight into the processes underlying recovery following stroke or other forms of brain injury.

In an impressive series of experiments reported over the past decade Merzenich and his colleagues[2-4] have used multiple microelectrode recordings to map out the representation of the hand and individual digits in the somatosensory cortex of monkeys (Figure 1A). They have shown that these cortical sensory maps become reorganized following a variety of perturbations which change the relevant afferent signals. For example, transecting the peripheral nerve which supplies a specific digit, or amputating the digit causes the area of cortex receiving sensory input from that finger to fall silent.[2,3] After a short period of time, however, this dormant cortical tissue begins responding to stimulation of the physically and representationally adjacent fingers. In other words, the representations of the skin surfaces in the surrounding area of cortex expand and come to occupy the site which has been deafferented by the peripheral nerve transection (Figure 1B). Similar changes to somatotopic representations within the sensory cortex have also been observed following artificial syndactyly[5] and transfer of innervated "skin islands".[6]

Donoghue and coworkers[7,8] have performed an analagous series of experiments in rats which have shown that the motor cortex also has the capability to undergo plastic reorganization following peripheral manipulations. Using intracortical microstimulation techniques, they have mapped the areas of cortex which control movement of the forelimb, face, and vibrissae. If the forelimb is then amputated or the lower branches of the facial nerve which innervate the vibrissae are sectioned, the cortical maps become altered so that microstimulation of areas which have lost their peripheral targets now produces movements of adjacent structures. For example, after forelimb amputation the cortical area that evokes shoulder movements increases in size to occupy the former forelimb representational area.

Similar results have been obtained in humans using transcranial magnetic stimulation to map cortical areas from which

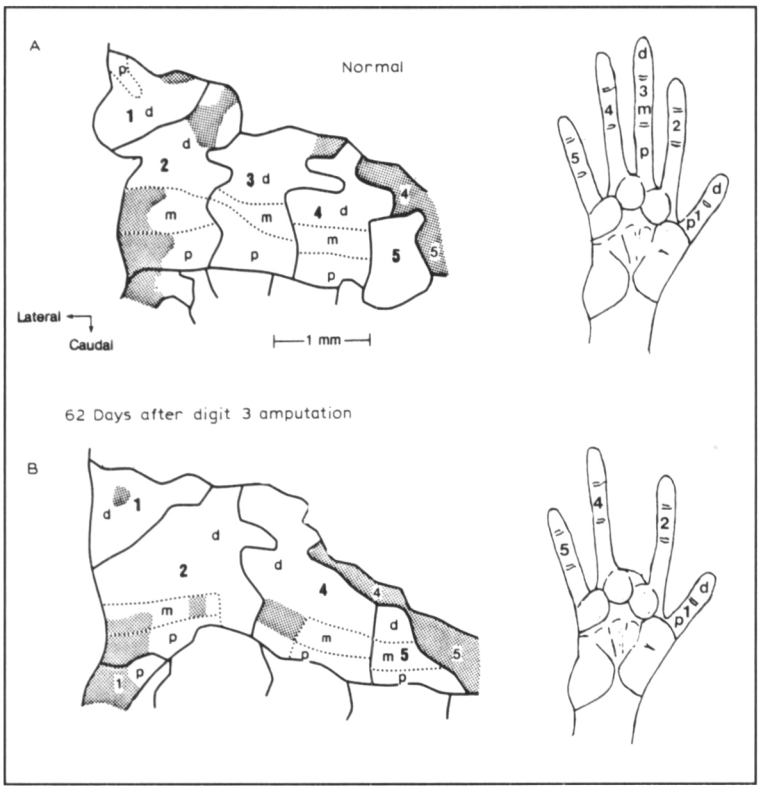

Figure 1: ***A****. Map of a portion of the somatosensory cortex in an adult owl monkey showing areas where each of the digits of the contralateral hand are represented. The map was generated following multiple microelectrode penetrations to identify location of neurons responding to stimulation at different sites on the hand and fingers.* ***B.*** *Cortical map from the same region of the same monkey 62 days after amputation of digit 3. Note that the cortical representations for digits 2 and 4 have expanded to occupy most of the area of cortex where digit 3 was previously represented. (Adapted from Jenkins and Merzenich 1987 – reference 12 – with permission).*

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motor responses can be elicited in different body parts. In forearm amputees motor evoked potentials from muscles proximal to the amputation are substantially larger than those from homologous muscles on the opposite side.[9,10] In addition the responses from the side of the amputation can be obtained with stimulation over a wider area of cortex and the stimulus intensity required to elicit these responses is lower than on the other side. In normal subjects similar short term changes in responses to magnetic stimulation occur following transient ischaemic deafferentation of the forearm.[11]

The available evidence, then, appears to support the notion that alterations in cortical representational somatotopy occur following manipulations in the periphery. Are similar changes apparent after central manipulations? Relatively few studies have addressed this issue directly, but Jenkins and Merzenich[12] described changes in cortical sensory maps in monkeys following ablation of the area of sensory cortex representing one finger. Skin surfaces formerly represented at the site of the lesion came to be represented in the surrounding intact cortical tissue. Further evidence for functional reorganization following localized cortical lesions has been provided by a behavioural study in rats.[13] Animals were trained to press a bar with their forelimb to avoid an electric shock. The forelimb area of motor cortex was then excised. There was a transient deterioration in performance (latency to bar press), but with further training the animals soon reacquired the ability to use the forelimb. Interestingly, the expression of c-fos, an immediate early gene associated with neuronal stimulation,[14] was markedly increased in the hindlimb motor cortex of animals which recovered. If a second lesion was then made in the hindlimb area of motor cortex, the original deficit reappeared, suggesting that the functional recovery had occurred as a result of transfer of forelimb control to the hindlimb area.

More recently, studies using positron emission tomography (PET) have shown analogous representational changes in the cortical motor areas of human subjects who have recovered hand function following infarcts in the posterior limb of the internal capsule.[15] In particular a ventral extension of the hand field into the area of cortex normally controlling the face was observed.

Thus, it appears likely that cortical plasticity can account for some of the recovery of function that is observed following damage to the cortex or its efferent pathways. The time course over which this plasticity occurs provides insight into the underlying mechanisms. In the experiments performed on monkeys by Merzenich and coworkers[2] there was an interval of several weeks between the experimental manipulation and the repeat cortical mapping. This time period would certainly be sufficient to allow for neuronal sprouting and formation of new synapses, although it is possible that other mechanisms such as unmasking contributed to the plastic changes in these models. However, Donoghue et al.[7] found that intracortical stimulation in the vibrissa representational area of the motor cortex elicited forelimb EMG activity in rats after an average of only 95 minutes following acute facial nerve transection. Similarly, Recanzone et al.[16] demonstrated that the area of receptive fields in the somatosensory cortex of cats is altered within 1-2 hours following peripheral nerve stimulation.

It seems unlikely that sprouting and new synapse formation could account for the rapid changes observed under these conditions. A more plausible explanation is that the synapses already exist, but are normally ineffective or weak. Given the proper conditions, however, such synapses may become unmasked or disinhibited and subsequently start to influence cortical activity. Evidence from both anatomical and neurophysiological studies appear to support this hypothesis. In particular, it is known that pyramidal cells within the sensorimotor cortex possess axon collaterals which extend laterally and have synapses on inhibitory interneurons.[17,18] Furthermore, these interneurons appear to be GABAergic in nature: intracortical microstimulation within the sensorimotor cortex of rats following local application of GABA antagonists evokes movements in body parts represented both at the site of stimulation as well as those represented in adjacent areas.[19] Because these applications led, in effect, to functional expansions of the cortical representational areas, Jacobs and Donoghue[19] suggested that this disinhibition mechanism may account for the similar changes observed following nerve lesions. To show that this is the case, there would have to be evidence that nerve lesions (or other manipulations) lead to modulations in intracortical inhibition. Such evidence is indirectly available: GABA activity is down- or up-regulated following sensory deprivation[20] or stimulation,[21] respectively. Furthermore, Sanes and Donoghue[22] report that there is a 20% drop in the number of GABA stained neurons in the motor cortex contralateral to a facial nerve lesion. If such alterations are accompanied by changes in the effectiveness of local inhibitory circuits, then this mechanism may be at the root of the reorganization in representational somatotopy observed following the manipulations described previously, including those occurring after cortical lesions.

Use of Alternate Descending Pathways on the Lesioned Side

When large areas of cortex are damaged there may not be sufficient surviving tissue around the affected site to allow somatotopic reorganization of the type described above. In these situations, it is more likely that representations will shift to areas which are closely related functionally but which may not be in close physical proximity. That is, a shift in the hierarchical organization of the system will occur. This is theoretically possible because of the relatively high degree of redundancy within the motor system, illustrated by the parallel and independent organization of the inputs to and outputs from cortical motor areas.[23] Strick[24] has shown that, at least for the hand representation, the primary motor cortex, premotor cortex, and supplementary motor area (SMA) receive separate subcortical inputs from the cerebellum and basal ganglia via the ventrolateral thalamus. Each also receives preferential input from different regions of the parietal cortex. Previously it was believed that the principal outputs from premotor cortex and SMA were directed to the primary motor cortex, but it is now known that these areas have direct projections to brainstem regions involved in motor control[25] and to the cervical regions of the spinal cord.[26] These parallel efferent pathways descend through different regions of the internal capsule: fibres from the motor cortex travel through the posterior limb; those from the premotor cortex occupy the genu; whereas, those originating in the supplementary motor area descend via the anterior limb.[27] Thus, each cortical motor area has independent inputs from subcortical and parietal lobe

systems, and each appears to have a relatively independent pathway for descending control of the spinal cord and muscles. This may partially account for recovery of motor function in patients who have had capsular infarcts with imaging studies showing what appears to be complete destruction of the part of the posterior limb of the internal capsule which contains the major efferent projections from primary motor cortex (i.e., the corticospinal tract).

Evidence that the SMA may take on new functions following damage to the primary motor cortex has been presented by Aizawa and colleagues.[28] These researchers measured neuronal activity in the SMA of a monkey during an overlearned simple keypress movement before and after a lesion to the motor cortex. During the learning period many neurons in the SMA exhibited task related changes in their firing patterns, but this activity eventually disappeared after extensive training (12 months). However, following a lesion to the motor cortex, task related neuronal activity reappeared in the SMA. One might suspect that if the motor cortex and its efferent projections had been extensively damaged that motor commands were reaching the spinal cord from the SMA via alternative descending pathways.

Role of Uncrossed Motor Pathways and the Hemisphere Ipsilateral to a Hemiplegia

As many as 25% of fibers in the corticospinal tract of humans and primates do not cross in the decussation of the pyramids at the level of the lower medulla.[29] Some of these do subsequently cross at a lower level in the spinal cord, but 10 - 15% of corticospinal tract fibers descend uncrossed in the anterior or lateral columns of the spinal cord and may play some role in controlling movement of the body on the same side as the cerebral hemisphere from which they originated. Could these uncrossed motor pathways contribute to recovery of function following unilateral cerebral damage?

Evidence that uncrossed motor pathways can play an important functional role comes from several well documented patients who had complete removal of an entire cerebral hemisphere (usually to control intractable epilepsy) without developing significant hemiplegia.[30] Of course, the resected hemisphere in most of these cases had probably been highly abnormal since birth or early childhood, so there would have been many years for the other hemisphere to assume control of the ipsilateral limbs. In contrast, careful clinical examination of previously healthy patients who have suffered a stroke affecting one cerebral hemisphere may reveal mild weakness and impairment of fine motor skills in the "unaffected" arm.[31,32] In detailed self observations following his own stroke which resulted in a left hemiplegia, Brodal[33] described problems with writing and other skilled tasks using the right hand, suggesting that the lesion which in this case was in the right cerebral hemisphere had damaged pathways which normally contribute to control of some movements of the ipsilateral upper extremity.

If uncrossed pathways from the undamaged hemisphere contribute significantly to recovery from hemiplegia, then a second stroke affecting this hemisphere should cause not only a contralateral hemiplegia but also reappearance of the neurological deficit on the recovered side. Clinical and pathological details concerning three patients who showed this sequence of events have been reported by Miller Fisher.[34] We have recently seen a similar patient in our institution – a 48-year-old hypertensive male who initially had an intracerebral hemorrhage into the left capsular area resulting in a severe right hemiplegia. He gradually improved, although a mild right spastic hemiparesis persisted. Three years after the first stroke he had a second small hemorrhage in an almost identical location in the right hemisphere (Figure 2). This resulted in a very mild sensorimotor deficit in the left arm, but what was much more striking was a marked worsening of the right hemiparesis. The most plausible explanation for this is that motor fibers passing through the site of the new hemorrhage in the right internal capsule must have played a role in the recovery from the previous right hemiplegia.

Recent studies using positron emission tomography (PET) to examine patients who have recovered from paresis of an upper extremity due to a capsular infarct have provided further evidence

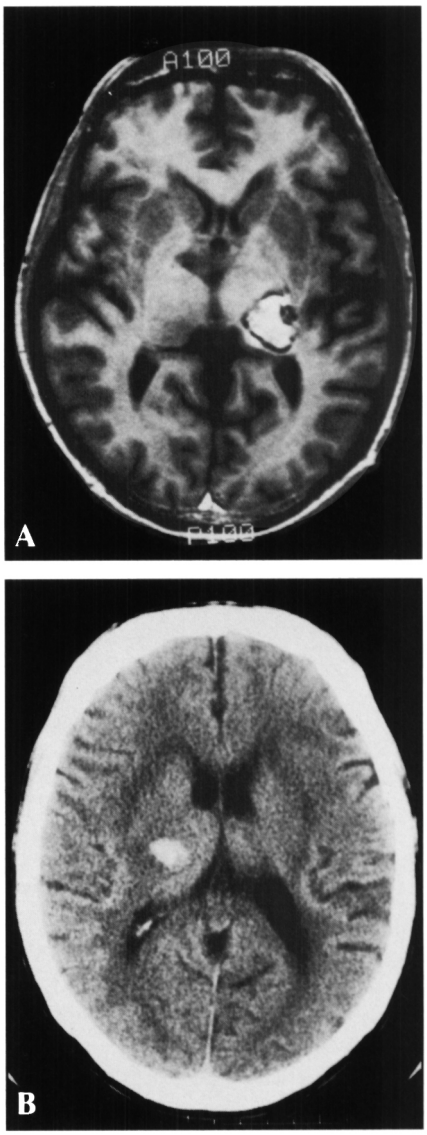

Figure 2: ***A.*** *MRI scan showing an intracerebral hemorrhage involving the posterior limb of the left internal capsule.* ***B.*** *CT scan on the same patient 3 years later showing a hemorrhage in the right internal capsule. This was accompanied by a marked worsening of the residual deficits in the right arm and leg which had persisted after the initial stroke.*

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suggesting that ipsilateral motor centers may play a role in recovery from hemiplegia.[35-37] PET scans were obtained while the subjects performed a semi-skilled motor task (sequential thumb - finger opposition). In normal subjects and in patients using their unaffected hand the PET scan showed evidence of increased regional blood flow, and presumably increased local metabolic activity, in the contralateral motor cortex and premotor regions and in the ipsilateral cerebellum. However, when the patients used the previously paretic hand, regional cerebral blood flow was increased not only in the contralateral cerebral hemisphere but also in several motor areas of the ipsilateral hemisphere. The initial study reporting this observation was based on averaged data from several patients. Further developments in the techniques to analyse PET data have made it possible to examine changes in individual subjects, and it has become apparent that the increased activation in the ipsilateral hemisphere is not so consistent as initially believed. Rather, there is considerable individual variation in the patterns of activation of both the ipsilateral and contralateral hemispheres following recovery from a hemiparesis.[15]

Assuming that the undamaged hemisphere can take over some of the control of the hemiplegic limbs following an infarct or hemorrhage in the other hemisphere, what mechanisms might allow this to happen, and why does it not occur more commonly and more effectively? There is evidence that transcallosal projections from the cortex of one hemisphere to homologous regions of the opposite hemisphere are predominantly inhibitory.[38] Damage to the cortex of one hemisphere might conceivably lead to disinhibition of cortical motor areas in the opposite hemisphere. Perhaps this is part of the physiological basis for the phenomenon of "unmasking". One could speculate concerning therapeutic interventions which might facilitate this process – e.g., localized delivery of a GABA antagonist to appropriate areas, providing that a suitable agent was available which did not produce unacceptable side effects on other parts of the CNS.

It should be noted that there are some clinical and experimental observations which suggest that control of ipsilateral limbs via uncrossed motor pathways may play only a small role in functional recovery in the majority of stroke patients. The motor deficits in the limbs ipsilateral to a hemisphere infarct, although detectable with sophisticated examination techniques, are very mild in most cases. Transcranial magnetic stimulation studies in normal subjects have suggested that only the trunk and jaw muscles are controlled from the ipsilateral hemisphere,[39] although a recent report[40] does provide some evidence for activation of ipsilateral limb muscles with magnetic stimulation. Another study using magnetic stimulation and EMG recording of single motor units in patients who had recovered following stroke found no evidence that motoneurons controlling the biceps muscle in the previously paretic arm were receiving excitatory inputs from the ipsilateral hemisphere.[41] However, Fries et al.[42] showed that transcranial magnetic stimulation over the motor cortex of the affected hemisphere in patients who had recovered from hemiplegia following capsular infarcts elicited bilateral EMG responses from the intrinsic hand muscles. They suggested that this may be due to the presence of bilateral polysynaptic corticoreticulospinal projections that bypass the site of the lesion in the internal capsule.

Motor Learning and Recovery of Function

The learning of new motor skills with an intact CNS and the recovery of previously learned motor skills that have been lost following localized damage to the CNS appear to be similar in several respects. In each case, the movements are initially highly variable and inaccurate, but with time and practice they become much more controlled and precise. The underlying neurophysiological modifications reponsible for these behavioral changes may be the same for motor learning and for recovery of motor skills following brain injury. Indeed, at a neuronal level motor learning may be considered to represent a very specific example of cortical plasticity. Thus, a knowledge of the basic mechanisms underlying motor learning may lead to a better understanding of the mechanisms operating during the recovery period following a stroke.

Asanuma and Keller[43] have shown that long-term potentiation (LTP), a phenomenon which has been studied extensively in the hippocampus as a possible model for memory, can occur in the motor cortex and may be one of the mechanisms underlying motor learning. In experiments on cats and monkeys they demonstrated that LTP can be induced in motor cortical neurons by tetanic stimulation delivered either to the somatosensory cortex alone or to the somatosensory cortex and thalamus together. Thus, the excitability of motor cortical neurons can be modified by increasing the magnitude of the input from corticocortical and thalamocortical afferents. The motor cortex receives inputs from these same areas during voluntary movements, including movements that are just being learned. Therefore, it is possible that LTP may play a role in motor learning by increasing the synaptic efficacy of motor cortical cells whose activity is most closely associated with the required output. A link between LTP and motor learning has not yet been demonstrated directly, but there is other experimental evidence showing that changes in neuronal activity within the motor cortex underlie modified motor output. For example, in cats that have undergone eye blink conditioning there is increased excitability of motor cortical neurons which are activated in association with the response.[44] Thus, it seems likely that the activity of motor cortical cells does undergo modulation during the process of learning new motor skills.

Whether analogous processes underlie recovery of motor function following stroke is open to speculation. However, as mentioned previously, expression of c-fos is increased in the forelimb sensorimotor cortex of rats following the learning of a conditioned lever pressing task. Similar increases in c-fos expression occur in the hindlimb sensorimotor cortex during recovery of this function following lesions of the forelimb cortical areas.[13] Taken together, these results suggest that, at least at this level, the mechanisms responsible for motor learning and functional recovery are similar.

There is also evidence from experiments on human subjects for increased activation of relevant areas of cortex during acquisition of a new motor skill. During learning of a complex sequential hand task there is increased regional cerebral blood flow in the contralateral supplementary motor area.[45] As subjects learn a repetitive sequence of finger movements, there is an increase in amplitude of motor evoked potentials (MEPs) from muscles participating in the task elicited by transcranial magnetic stimulation over the motor cortex.[46] However, by the time the subjects are able to accurately reproduce the sequence from memory the magnitude of the MEPs returns to the prelearning levels.

Therapeutic Implications and Future Experiments

With the evidence that a certain amount of plastic reorganization can occur following stroke or other forms of brain injury, and that this may be reponsible for some of the functional recovery that occurs in these situations, it is natural to ask what might be done to promote or facilitate these changes. Are any of the techniques currently being used in stroke rehabilitation having an influence on these mechanisms? Do repeated passive movements of an extremity or specific exercise programs lead to modulation of synaptic efficacy or reorganization of neuronal circuitry in the sensorimotor cortex or other areas? Could application of certain trophic factors or substances which block inhibitory neurotransmission facilitate the "unmasking" which seems to be responsible for some of the functional reorganization observed experimentally? What compounds might be used? Where should they be applied, and how can they be delivered to appropriate sites without producing undesirable side effects? It is conceivable that, as is the case during development, there is a critical time window during which experimental manipulations are capable of inducing plastic changes. If this is the case then the timing of therapeutic interventions following stroke will be extremely important.

There are obviously many other critical questions which must be addressed before any of these approaches can be considered for application in human stroke patients, and more work must be done with appropriate chronic animal models of stroke. But the important message is that the potential does exist for a considerable amount of functional recovery to occur, and the challenge is to discover ways and means of influencing these processes.

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