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NERVOUS SYSTEM REORGANIZATION FOLLOWING INJURY

R. CHEN,[1] L. G. COHEN* and M. HALLETT

Human Cortical Physiology Section and Human Motor Control Section, Medical Neurology Branch, National Institutes of Neurological Disorders and Stroke, National Institutes of Health Building 10, Room 5N226, 10 Center Drive MSC 1428, Bethesda, MD 20892-1428, USA

Abstract—Contrary to the classical view of a pre-determined wiring pattern, there is considerable evidence that cortical representation of body parts is continuously modulated in response to activity, behavior and skill acquisition. Both animal and human studies showed that following injury of the peripheral nervous system such as nerve injury or amputation, the somatosensory cortex that responded to the deafferented body parts become responsive to neighboring body parts. Similarly, there is expansion of the motor representation of the stump area following amputation. Reorganization of the sensory and motor systems following peripheral injury occurs in multiple levels including the spinal cord, brainstem, thalamus and cortex. In early-blind subjects, the occipital cortex plays an important role in Braille reading, suggesting that there is cross-modal plasticity. Functional recovery frequently occurs following a CNS injury such as stroke. Motor recovery from stroke may be associated with the adjacent cortical areas taking over the function of the damaged areas or utilization of alternative motor pathways. The ipsilateral motor pathway may mediate motor recovery in patients who undergo hemispherectomy early in life and in children with hemiplegic cerebral palsy, but it remains to be determined if it plays a significant role in the recovery of adult stroke. One of the challenges in stroke recovery is to identify which of the many neuroimaging and neurophysiological changes demonstrated are important in mediating recovery. The mechanism of plasticity probably differs depending on the time frame. Rapid changes in motor representations within minutes are likely due to unmasking of latent synapses involving modulation of GABAergic inhibition. Changes over a longer time likely involve other additional mechanisms such as long-term potentiation, axonal regeneration and sprouting. While cross-modal plasticity appears to be useful in enhancing the perceptions of compensatory sensory modalities, the functional significance of motor reorganization following peripheral injury remains unclear and some forms of sensory reorganization may even be associated with deleterious consequences like phantom pain. An understanding of the mechanism of plasticity will help to develop treatment programs to improve functional outcome. © 2002 Published by Elsevier Science Ltd on behalf of IBRO.

Key words: plasticity, reorganization, cortex, amputation, nerve injury.

It is a common clinical observation that functional recovery frequently occurs following a nervous system injury such as stroke, although the extent of recovery is highly variable. Some patients with initial severe hemiparesis may eventually achieve full recovery, while others have little or no improvement and remain severely disabled. There are many reasons for the different degrees of recovery, including age of the patient, location and extent of the lesion as well as individual variations in anatomical and functional connections. An understanding of the mechanisms underlying functional recovery is crucial to develop treatment programs to improve functional outcome.

There is now considerable evidence that cortical representation of body parts is continuously modulated in response to activity, behavior and skill acquisition (Kaas, 1991; Donoghue et al., 1996). Reorganization of cortical representation also occurs following a peripheral injury such as amputation or a brain injury such as stroke. These changes in plasticity may account for recovery of function after injury. While it is likely that some of the reorganization following injury takes place in the cortex, plastic changes may also occur in subcortical structures such as the thalamus, brainstem or spinal cord.

In this chapter, we will review the reorganization of the CNS following injury. We will first describe reorganization following peripheral injury and consider where in the CNS these changes take place. We then highlight the reorganization after different types of injury to the CNS. This is followed by a discussion of the possible mechanisms involved and the effects of age on these changes. Finally, we examine the functional significance of these changes.

REORGANIZATION FOLLOWING PERIPHERAL INJURY

Transient deafferentation

Transient deafferentation can induce rapid reorganization of the adult CNS and is a useful model to study short-term plasticity changes. During epidural nerve block, neurons in the cat primary somatosensory cortex (S1) that originally responded to stimulation of the anes-

[1] Present address: Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada.

*Corresponding author. Tel.: +1-301-496-9782; fax: +1-301-402-1007.

E-mail address: lcohen@codon.nih.gov (L. G. Cohen).

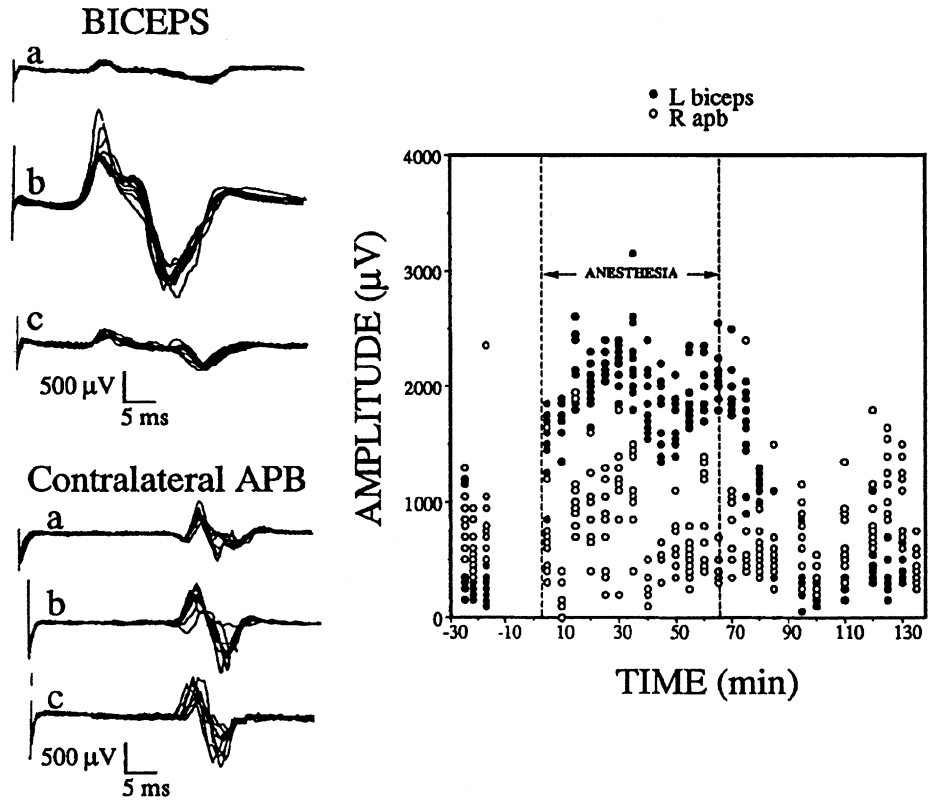

Fig. 1. Effects of transient deafferentation of the forearm in one subject. Deafferentation was induced by a tourniquet placed below the left elbow in combination with regional nerve block of the forearm and hand with administration of lidocaine. Ten superimposed MEPs from TMS before anesthesia (a), during anesthetic block (b) and after anesthesia (c) recorded from the left biceps and right (contralateral) abductor pollicis brevis (APB) muscles are shown on the left. MEP amplitudes from the left biceps and right APB muscles as a function of time course of the experiment are shown on the right. The biceps MEP amplitudes increased during anesthesia and returned to baseline level within 20 min after termination of anesthetic block. The contralateral APB MEP amplitudes were unchanged throughout the experiment. Modified from Brasil-Neto et al. (1992).

thetized area became responsive to stimulation of adjacent, unanesthetized areas. These changes reversed 2–4 h after the nerve block (Metzler and Marks, 1979). The findings suggest that cortical representation is dynamically modulated based on the pattern of afferent input.

We studied the effects of transient deafferentation of a limb in humans in a series of experiments (Brasil-Neto et al., 1992, 1993; Sadato et al., 1995; Corwell et al., 1997). Deafferentation was induced by regional anesthesia or ischemic nerve block with inflation of a blood pressure cuff above systolic blood pressure. Within minutes after the onset of deafferentation, the motor-evoked potential (MEP) amplitude elicited by transcranial magnetic stimulation (TMS) in the muscle immediately proximal to deafferentation increased several folds, then returned to control values within 20 min after termination of ischemia, suggesting that motor cortex excitability was increased during deafferentation (Fig. 1). The number of scalp positions that focal TMS could elicit responses in the muscle immediately proximal to ischemic block was also increased, which may be due to expansion of muscle representation or increased excitability of the motor system (Brasil-Neto et al., 1993). Positron emission tomography (PET) studies showed that during forearm ischemia, resting regional cerebral blood flow (rCBF) was increased in the sensorimotor cortex (SM1) bilaterally, suggesting that increased excitability of the motor cortex was associated with increased in synaptic activity (Sadato et al., 1995). In addition, there was a reduction in the rise of rCBF in the supplementary motor area (SMA) with flexion-extension movements of the elbow during forearm ischemia compared to movements without ischemia (Sadato et al., 1995). A possible explanation for this reduced rise of rCBF in the SMA is that deafferentation may induce disinhibition in the motor cortex through diminished of γ-aminobutyric acid (GABA)ergic activity, making cells there more excitable. Since cortical motoneurons are easier to activate, less excitatory synaptic drive from the SMA is necessary for the same movement.

Studies in humans with magnetoencephalography (MEG) also showed that rapid changes in somatosensory representation occur with deafferentation. Somatosensory-evoked fields produced by finger stimulation can be altered by transient ischemic deafferentation of the adjacent fingers. The representation of the stimulated finger shifted toward the representation of the deafferented fingers (Rossini et al., 1994).

Amputation and peripheral nerve lesions

Animal studies. Plasticity of the somatosensory sys-

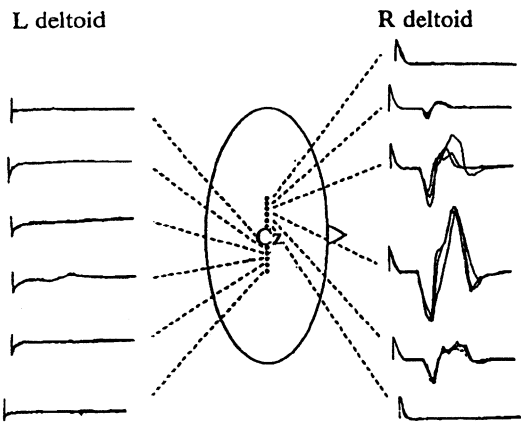

Fig. 2. Schematic diagram of the head of a right above-elbow amputee. Electromyogram responses from the deltoid muscles evoked by TMS with a focal figure-of-eight coil at equal stimulus intensities from different scalp positions 1 cm apart along the coronal axis are shown. Stimulation at four positions evoked responses from the deltoid muscle on the amputated side, whereas stimulation at only 1 position evoked responses from the deltoid muscle on the intact side. Modified from Cohen et al. (1991a).

tem has been studied extensively, and dramatic changes in the organization map of the S1 occur after removal of afferent input. Following peripheral nerve lesion or digit amputation in adult monkeys, parts of the S1 that previously responded to the deafferented body parts became responsive to inputs from neighboring body parts (Kelahan et al., 1981; Merzenich et al., 1983). These changes can be reversed after nerve regeneration (Wall et al., 1983). Although initial studies suggested that the upper limit of cortical expansion is 1–2 mm (Merzenich et al., 1983), corresponding to the projection zone of single thalamocortical axons, it is now known that long-standing amputation may result in cortical reorganization over a distance of up to 14 mm (Pons et al., 1991; Manger et al., 1996). Fusion of the skin of two adjacent digits in adult monkeys also led to reorganization of somatosensory representations. The cortical representation of the fused fingers in the S1 changed from the normal discontinuity between two fingers to a more continuous representation resembling one finger (Allard et al., 1991). Similar changes in the S1 with amputation have also been demonstrated in other animals such as cats, raccoons, rodents and bats (see Kaas, 1991 for review).

In the motor system, changes in cortical representation also occur after peripheral injury. Following amputation or peripheral nerve lesions, the area from which stimulation evoked movements of the adjacent body parts enlarged and the threshold for eliciting these movements was reduced (Donoghue and Sanes, 1988; Sanes et al., 1990). These changes began within hours after the motor nerve lesion (Sanes et al., 1988; Donoghue et al., 1990).

Human studies. In humans, reorganization of the somatosensory and motor systems also occurs following amputation. Sensations in the phantom limb can be elicited by somatosensory stimulation of the face and upper body in upper-limb amputees (Ramachandran et al., 1992), suggesting that the somatosensory representations of the face and upper body may have expanded to occupy the arm and hand area. This was supported by MEG studies which revealed medial displacement of the face area toward the hand representation in the somatosensory cortex (Elbert et al., 1994; Flor et al., 1995). The extent of shift in cortical representation correlated with the amount of phantom (Flor et al., 1995; Knecht et al., 1996). In the motor system, TMS studies demonstrated that for both upper- and lower-limb amputees, resting MEPs can be elicited at lower intensities (Hall et al., 1990; Cohen et al., 1991a; Chen et al., 1997a) and from more scalp positions (Cohen et al., 1991a; Fuhr et al., 1992) in muscles immediately proximal to the site of amputation compared to the homologous muscle on the normal side (Fig. 2). TMS also recruited a higher percentage of the motoneuron pool in the muscle on the amputated side than on the normal side (Cohen et al., 1991a; Fuhr et al., 1992). These results suggested that the excitability of the motor system projecting to the muscle immediately above the amputation is increased. Cortical reorganization was also demonstrated by PET studies that showed increased rCBF in the contralateral sensorimotor cortex with movement of the amputated side compared to the normal side in congenital and traumatic upper-limb amputees (Kew et al., 1994).

Cortical reorganization also occurs in humans after peripheral nerve lesions. In patients with facial palsy, TMS and PET studies reveal an enlargement of the hand representation with medial extension into the site of the presumed face area (Rijntjes et al., 1997). In patients who had anastomosis of musculocutaneous and intercostal nerves as treatment for traumatic cervical root avulsion, TMS mapping studies over several years showed that the biceps representation moved laterally from the intercostal area to the arm area. It appeared that immediately following the operation, the biceps muscle was controlled by the intercostal area of the motor cortex, but with time, the original biceps area could access the biceps muscle via the intercostal nerve. This change in cortical representation is likely to be functionally significant since it was associated with improved elbow flexion control and independence of biceps motor unit discharge from respiration (Mano et al., 1995).

The site of reorganization following peripheral lesions

Changes in cortical maps following a peripheral lesion may be the result of reorganization at cortical or subcortical levels. There is evidence that reorganization can occur at multiple levels including the cortex, thalamus, brainstem, spinal cord and peripheral nerves. After chronic partial digit amputation in monkeys, there was both increased branching of the severed digital nerve and increased innervation density in the stump. It was suggested that the stump may be innervated by neurons that previously had innervated the amputated digit, which may explain the expansion of the cortical map of the stump (Manger et al., 1996). In monkeys with hand amputation, afferent terminations from the forearm were found to extend into the hand areas of the dorsal

horn of the spinal cord and the cuneate nucleus in the medulla (Florence and Kaas, 1995), providing some evidence for sprouting at the level of the spinal cord and brainstem. Plasticity changes have also been demonstrated in the thalamus, where neuronal recordings that local anesthesia induced immediate and reversible reorganization of the ventral posterior medial nucleus (Nicolelis et al., 1993). Long-term dorsal rhizotomies in monkeys resulted in transneuronal degeneration of nonnociceptive somatosensory pathways and increased activity of thalamic cells innervated by pain afferents (Rausell et al., 1989). In other situations, reorganization may occur mainly within the cortex. One such example is the increased receptive field size in the visual cortex after a retinal lesion, which cannot be sufficiently accounted for by changes in the lateral geniculate nucleus (Gilbert and Wiesel, 1992). These changes may arise through modifications in synaptic coupling of the extensive intrinsic cortical connections (DeFelipe et al., 1986; Huntley and Jones, 1991; Kaas, 1991; Donoghue and Sanes, 1994). It appears that plasticity changes in the somatosensory system can occur at multiple cortical and subcortical sites, whereas in the visual system reorganization mainly is in the cortex (Kaas and Florence, 1997).

We investigated the site of motor reorganization following amputation in humans by stimulating the nervous system at different levels with TMS, transcranial electrical stimulation (TES), spinal electrical stimulation (SES) and measurement of the maximum H-reflex/M-wave (H/M) ratio (Fuhr et al., 1992; Brasil-Neto et al., 1993; Chen et al., 1997a). TMS at low intensities predominately activates pyramidal tract neurons via cortical interneurons and is dependent on motor cortex excitability, whereas TES predominately activates pyramidal tract axons directly and is little affected by cortical excitability (Day et al., 1989; Amassian et al., 1990; Rothwell et al., 1991; Thompson et al., 1991; Nakamura et al., 1996). SES activates the descending motor tracts in the spinal cord while the H/M ratio is a measure of spinal motoneuron excitability. In lower-limb amputees, the threshold of TMS activation for the muscle just proximal to the amputation was decreased compared to the homologous muscle on the normal side, while the TES threshold was similar on the two sides. The percentage of the motoneuron pool activated by TMS was higher on the amputated side but that activated by SES was similar on the two sides (Chen et al., 1997a). The maximum H/M ratio did not differ on the two sides (Fuhr et al., 1992). These results showed that while excitability of the motor system to TMS is increased on the amputated side, excitability of subcortical and spinal structures was unchanged, suggesting that motor reorganization following amputation occurs predominately at the cortex.

We also found similar changes with transient deafferentation induced by ischemic nerve block. MEP amplitude was increased for TMS but not for TES nor SES, and there was no change in the maximum H/M ratio (Brasil-Neto et al., 1993). Thus, motor reorganization following transient deafferentation also occurs predominately in the cortex.

REORGANIZATION ASSOCIATED WITH RECOVERY FROM STROKE

Stroke is the third leading cause of death in the United States and is the main cause of long-term disability among adults. Spontaneous recovery usually occurs, although the extent is highly variable. Multivariate analysis suggested that the best predictor of outcome after hemispheric stroke is the severity of initial neurologic deficit (Heinemann et al., 1987). Motor recovery occurs predominantly in the initial weeks to first three months, but can continue at a slower pace throughout the first year (Kotila et al., 1984; Kelly-Hayes et al., 1989).

Recovery in the first few days may be due to resolution of edema or reperfusion of the ischemic penumbra. Much of the recovery after the initial 2 weeks is likely due to brain plasticity, with some areas of the brain taking over the functions previously performed by the damaged regions. Proposed mechanisms of recovery include redundancy of brain circuitry with parallel pathways performing similar functions such that an alternative pathway may take over when another has been damaged, unmasking of previously existing but functionally inactive pathways, and sprouting of fibers from the surviving neurons with formation of new synapses (Lee and van Donkelaar, 1995). The mechanisms involved likely depend on the extent of injury. When damage to a functional system is partial, within-system recovery is possible, whereas after complete destruction, substitution by a functionally related system becomes the only alternative (Seitz and Freund, 1997).

Animal studies

Several studies examined the reorganization following small lesions of the primary motor cortex (M1) or the S1. Jenkins and Merzenich (1987) reported that after small infarcts of the S1 in owl monkeys, the skin surface formerly represented by the infarcted zone became represented topographically in the surrounding cortical region. This was associated with enlargement of the cutaneous receptive fields in the cortical areas surrounding the lesion, since the same cortical area now represented a larger skin area. However, the findings appear to differ in the motor system following a small M1 infarct in the digit representation. In monkeys not receiving post-infarct training, the movement formerly represented in the infarcted zone did not reappear in the adjacent cortical regions. In addition, the digit representation previously present in the areas adjacent to the infarcted cortex was further reduced (Nudo and Milliken, 1996). In contrast, monkeys which received 'rehabilitative training' following the infarct had a preserved hand territory, and in some cases, the hand territory expanded to the elbow and shoulder representations (Nudo et al., 1996). However, with or without post-infarct training, the monkeys recovered their hand functions. These findings showed that functional recovery after small cortical lesions may be associated with the adjacent cortical area taking over the function of the damaged cortex. The extent of reorganization may be limited by the extent of convergence and divergence of anatomical

inputs and outputs of the area (Jenkins and Merzenich, 1987). However, large lesions may involve different mechanisms. Recovery of function in monkeys with an M1 lesion but no post-infarct training demonstrated that assumption of lost functions by the adjacent undamaged motor cortex is not inevitable, but to some extent is use-dependent. Other cortical or subcortical motor areas may also mediate functional recovery. For example, there are changes in the SMA following M1 lesions. Neurons in the SMA are usually active before limb movement, but such pre-movement activity was no longer observed after the movement was extensively over-learned (Aizawa et al., 1991). However, after a focal M1 lesion, pre-movement activity in the SMA reappeared (Aizawa et al., 1991). A possible interpretation is that the movement became more difficult after the M1 lesion, leading to reappearance of SMA activity.

Human studies

Factors that determine the severity of deficits and degree of functional recovery. Several studies examined the factors that determine the severity of deficits and the extent of recovery. The influence of lesion size is controversial. In patients with middle cerebral infarcts, infarct size correlated with severity of motor weakness (Mohr et al., 1993). However, several other studies found little (Binkofski et al., 1996) or no (Pantano et al., 1996) correlation between outcome and infarct size. The location of the infarct may be more important. Poor motor recovery was associated with more severe damage to the pyramidal tract as measured with magnetic resonance imaging (MRI) (Binkofski et al., 1996) or lesion of the parietal lobe (Pantano et al., 1996). The importance of the pyramidal tract is also demonstrated by several TMS studies. TMS activates pyramidal-tract neurons and the MEP amplitude of hand muscles in response to stimulation of the lesioned cortex correlated with the extent of recovery of hand function (Binkofski et al., 1996; Rapisarda et al., 1996; Turton et al., 1996).

The role of the affected hemisphere in mediating stroke recovery. Motor recovery following damage to the motor cortex or the pyramidal tract may be mediated by the use of alternative cortical areas in the damaged hemisphere that can access spinal motoneurons. Two general mechanisms are possible here: the use of parallel, redundant pathways or new regions taking over the function of the damaged area. There are several parallel motor pathways in the motor system. In addition to the M1, motor areas have been identified in the premotor cortex, SMA and cingulate cortex (Dum and Strick, 1991). All these motor areas contain somatotopic representations and all contribute to the pyramidal tract (He et al., 1993, 1995). These parallel pathways may substitute for each other in recovery from hemiparesis (Fries et al., 1993). Patients with an infarct limited to the anterior or posterior limb of the internal capsule initially had severe motor deficits, but subsequently had excellent recovery. Patients with more extensive lesions of the internal capsule had poor recovery. Fries et al. (1993) also showed that, in the monkey, pyramidal-tract fibers from different cortical areas occupy discrete locations in the internal capsule, suggesting that recovery in patients with small lesions of the internal capsule may be mediated by undamaged, parallel motor pathways. Further support for the role of alternative motor pathways in functional recovery came from PET studies in patients with good recovery from striatocapuslar infarcts (Weiller et al., 1992, 1993). Compared to normal subjects, finger movements of the recovered hand showed greater activation of the anterior aspect of the insular and the inferior parietal cortex (Brodmann area 40), and both areas have direct connections to the premotor cortex (area 6) (Weiller et al., 1992, 1993). In some patients, movement of the recovered hand led to increased SMA activation, which may represent a correlate of the reorganization in SMA observed in monkeys with M1 lesions (Aizawa et al., 1991).

There is also evidence for the adjacent cortex taking over the function of the damaged pathways. In patients with lesions limited to the posterior limb of the internal capsule, recovered hand movement led to motor cortex activation that extended laterally to the face area, suggesting that the hand representation shifts toward the face area (Weiller et al., 1993). This change was not observed in patients with lesions in the anterior limb of the internal capsule (Weiller et al., 1993). This may be explained by sparing of the pyramidal tract from the face representation in patients with lesions confined to the posterior limb of the internal capsule, since the fibers destined for the face travel to more anterior locations in the internal capsule than fibers for the arm and leg (Hardy et al., 1979). Thus, the shift of cortical representation following amputation or peripheral nerve lesions may also be present with recovery from stroke. In our own PET studies in patients with subcortical infarct, there was increased activation of the contralateral sensorimotor area with finger movement compared to normal subjects (Wassermann, 1995). This suggests that the sensorimotor area was working vigorously to compensate for the lesion or additional sensorimotor cortex was recruited. Weiller et al. (1993) also found that the pattern of activation was highly variable among patients, which may reflect the differences in lesion location, size and individual variations in anatomical and functional connections.

The role of ipsilateral motor pathways. Several authors have raised the possibility that ipsilateral motor pathways play a role in functional recovery from stroke (Fisher, 1992; Lemon, 1993; Lee and van Donkelaar, 1995). Fisher (1992) described two patients with good recovery from a previous stroke, but hemiplegia reappeared on the recovered side after another pure motor stroke in the opposite hemisphere. Lee and van Donkelaar (1995) also reported a similar case. A transcranial Doppler study in patients with cortical ischemic stroke showed a greater increase in the flow velocity of the ipsilateral middle cerebral artery during movements of the recovered hand compared to the unaffected hand or normal controls, suggesting that the activ-

ity of the undamaged hemisphere with movement of the recovered hand was increased (Silvestrini et al., 1995). PET studies also showed changes in the unaffected hemisphere in recovered stroke patients. As a group, the stroke patients had significantly increased CBF in the ipsilateral SM1 with movement of the recovered hand but not with movement of the unaffected hand (Chollet et al., 1991; Weiller et al., 1992). However, a subsequent report from the same group using single-subject analysis found ipsilateral SM1 activation in only four out of eight patients, and these patients had mirror movements in the unaffected hand when they moved the recovered hand (Weiller et al., 1993). Therefore, it is unclear whether activation of the ipsilateral SM1 was related to recovery of function or simply secondary to mirror movements.

TMS has also been used to examine the ipsilateral corticospinal projection in patients who recovered from stroke. Palmer et al. (1992) recorded post-stimulus time histograms of single motor units from the biceps muscle in nine recovered stroke patients, and found no evidence that the ipsilateral fast corticospinal tract was responsible for the recovery. Turton et al. (1996) reported a longitudinal study of 21 stroke patients. Ipsilateral MEPs in the affected arm were more common and of longer latencies than those in the unaffected arm, and were observed mainly in the proximal muscles and occasionally in hand muscles. However, since ipsilateral responses were more common among stroke patients who had poor recovery than patients with good recovery, it is unclear whether they play any role in ensuing functional recovery. In contrast, Caramia et al. (1996) reported ipsilateral MEPs in hand muscles in 13 patients who had rapidly recovered from hemispheric stroke. The ipsilateral MEPs were elicited only with muscle activation and had higher thresholds, lower amplitudes but, surprisingly, shorter latencies compared to contralateral MEPs (Caramia et al., 1996). All these studies used large circular (Palmer et al., 1992; Caramia et al., 1996) or double-cone (Turton et al., 1996) magnetic coils. Palmer et al. (1992) and Turton et al. (1996) did not test high-intensity stimulations because that may activate the contralateral hemisphere. Since the thresholds for ipsilateral responses are considerably higher than those for contralateral responses (Wassermann et al., 1991, 1994), the contribution of ipsilateral MEPs may have been underestimated. In contrast, Caramia et al. (1996) may have activated the contralateral hemisphere with high-stimulus intensities. Therefore, the role of ipsilateral motor pathways in recovery from stroke remains unclear.

REORGANIZATION FOLLOWING CENTRAL LESIONS

Spinal cord injury

Several studies showed that spinal cord injury induced reorganization of the sensory and motor systems. In cats spinalized at T12 level at 2 weeks of age, the deafferented hindlimb region of the S1 was reorganized to a second map of the trunk and forelimb (McKinley et al., 1987). In humans, motor reorganization was demonstrated by TMS in patients with spinal cord injury. In the muscle immediately rostral to the level of injury, MEPs can be elicited from more scalp positions and TMS activated a higher percentage of the motoneuron pool than normal controls (Levy et al., 1990; Topka et al., 1991). This again points to increased excitability of the motor system projecting to the muscle immediately above the level of injury, similar to the findings in amputees. The site of reorganization after spinal cord injury has not been studied in detail. It is possible that cortical mechanisms are important, similar to the reorganization following amputation.

Hemispherectomy

Hemispherectomy is occasionally performed to treat intractable epilepsy or brain tumor. The pattern of central motor reorganization has been studied in hemispherectomy patients (Benecke et al., 1991; Cohen et al., 1991b; Hallett et al., 1993). In patients with early hemispherectomy, TMS of the healthy hemisphere produced ipsilateral MEPs at latencies similar to contralateral MEPs, with higher amplitudes in proximal than distal muscles (Benecke et al., 1991; Hallett et al., 1993). Both PET (Cohen et al., 1991b) and TMS (Cohen et al., 1991b; Hallett et al., 1993) studies showed that ipsilateral representations were topographically different from contralateral representations, with ipsilateral representations occupying more anterior and lateral locations than contralateral representations in the healthy hemisphere (Fig. 3). This is similar to the ipsilateral cortical motor representations for hand muscles in normal subjects, which also occupies a more lateral location than the representations for contralateral hand muscles (Wassermann et al., 1994). Patients with late hemispherectomy had ipsilateral MEPs of longer latencies and lower amplitudes, and had a worse outcome than the early hemispherectomy patients (Benecke et al., 1991; Hallett et al., 1993). These findings suggested that ipsilateral motor pathways may mediate recovery in patients who had undergone early hemispherectomy.

Cerebral palsy

Cerebral palsy refers to non-progressive neurological deficits in children and is usually due to focal brain injury that had occurred in utero or shortly after birth. Carr et al. (1993) studied the motor reorganization in children with hemiplegic cerebral palsy. They reported that in patients with congenital hemiplegia, intense mirror movements and relatively good functions of the affected hand, TMS of the unaffected M1 elicited short-latency MEPs from the ipsilateral first dorsal interosseous (FDI) muscle. These patients were considered to have suffered their brain insult before 29 weeks of gestation. In patients with good recovery of the affected hand without mirror movements, stimulation of the affected M1 elicited short-latency MEPs from the affected (contralateral) FDI muscle. Patients with no MEP, from the affected FDI with stimulation of the affected or the unaffected M1 all had poor hand func-

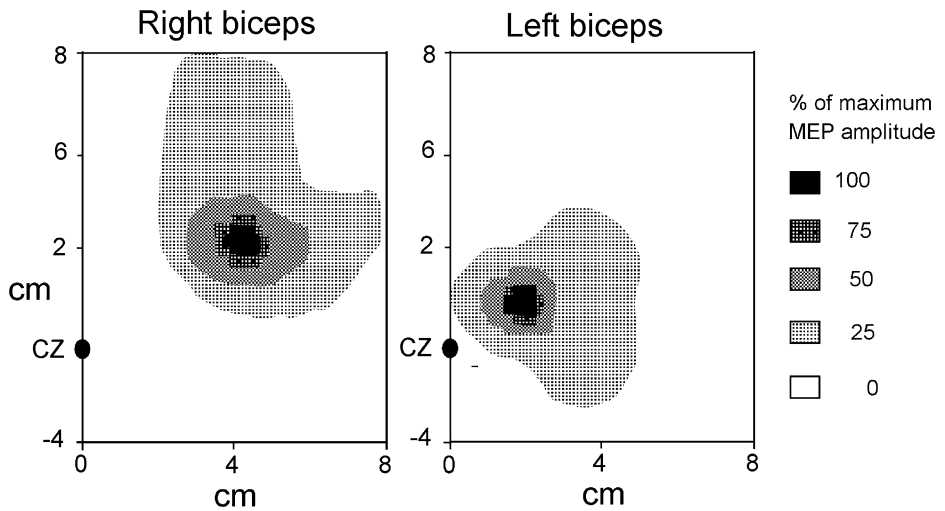

Fig. 3. Difference in topography for representations of contralateral and ipsilateral muscles. Data from a 32-year-old man with congenital left porencephalic cyst who had hemispherectomy at age 7. MEP amplitudes evoked by TMS with a focal figure-of-eight coil from different scalp positions are shown as percentages of the maximum MEP amplitude. The representation of the right (ipsilateral) biceps was anterior and lateral to that of the left (contralateral) biceps. CZ refers to the vertex in the international 10–20 system. Modified from Cohen et al. (1991b).

tions. Ipsilateral MEPs with prolonged latencies were found in some patients without mirror movements; these patients had variable degrees of recovery. Thus, it appeared that direct corticospinal projections, as shown by short-latency MEPs, are necessary for good recovery of hand functions and may arise from either the affected or the unaffected hemisphere. Ipsilateral motor pathways from the unaffected hemisphere may play a role in recovery from brain injury occurring early in life. Possible mechanisms include development of new ipsilateral corticospinal projections, double-crossing of contralateral corticospinal fibers, and reinforcement of existing ipsilateral corticospinal pathways. Ipsilateral MEPs of prolonged latency may be due to enhanced corticoreticulospinal pathway (Benecke et al., 1991). The importance of ipsilateral pathways in mediating recovery of function from brain injury early in life was also demonstrated in a fMRI study in patients with unilateral brain damage in the perinatal period. Finger movements of the affected hand produced widespread activation of the intact, ipsilateral hemisphere (Cao et al., 1991).

Cross-modal plasticity

Cross-modal plasticity refers to the concept that the cortex normally responsive to one sensory modality, when deprived of its usual input, may be responsive to inputs from other sensory modalities. Cross-modal plasticity has been most extensively investigated after visual loss. In normal cats, most of the neurons of the anterior ectosylvian visual area respond only to visual stimuli. By contrast, in cats visually deprived from birth, most cells in the anterior ectosylvian area reacted to auditory and somatosensory stimuli (Rauschecker and Korte, 1993). PET studies in subjects who became blind early in life showed that the primary visual cortex was activated by Braille reading (Sadato et al., 1996). This visual cortex activation is utilized in Braille reading by early-blind subjects, since repetitive TMS of the occipital cortex can disrupt Braille reading in the early-blind subjects, but not in normal-sighted volunteers (Cohen et al., 1997) (Fig. 4).

Visual deprivation also led to a compensatory increase in the representation of selective somatosensory inputs. In rats visually deprived from birth, the somatosensory cortex expands for facial vibrissae (barrel field) (Rauschecker et al., 1992) due to enlarged cell somata in the somatosensory cortex. In humans, somatosensory-evoked-potentials (Pascual-Leone and Torres, 1993) and TMS mapping (Pascual-Leone et al., 1993) studies showed expanded sensory and motor representations of the reading finger of Braille readers. These changes are likely related to increased training and use, supporting the idea that cortical representation is dynamically modulated based on learning and experience (Donoghue et al., 1996).

MECHANISMS OF CORTICAL REORGANIZATION

Mechanisms for short-term changes

The two main mechanisms proposed to explain reorganization after peripheral lesions are unmasking of previous present but functionally inactive connections and growth of new connections (collateral sprouting). Since the growth of new connections takes time, rapid expansion of muscle representation that occurs within minutes to hours following transient deafferentation in humans (Brasil-Neto et al., 1992, 1993; Sadato et al., 1995) or nerve lesions in animals (Merzenich et al., 1983; Donoghue et al., 1990; Nicolelis et al., 1993) likely involve unmasking of latent excitatory synapses.

Unmasking of latent synapses can be due to several mechanisms and include increased excitatory neurotransmitter release, increased density of postsynaptic recep-

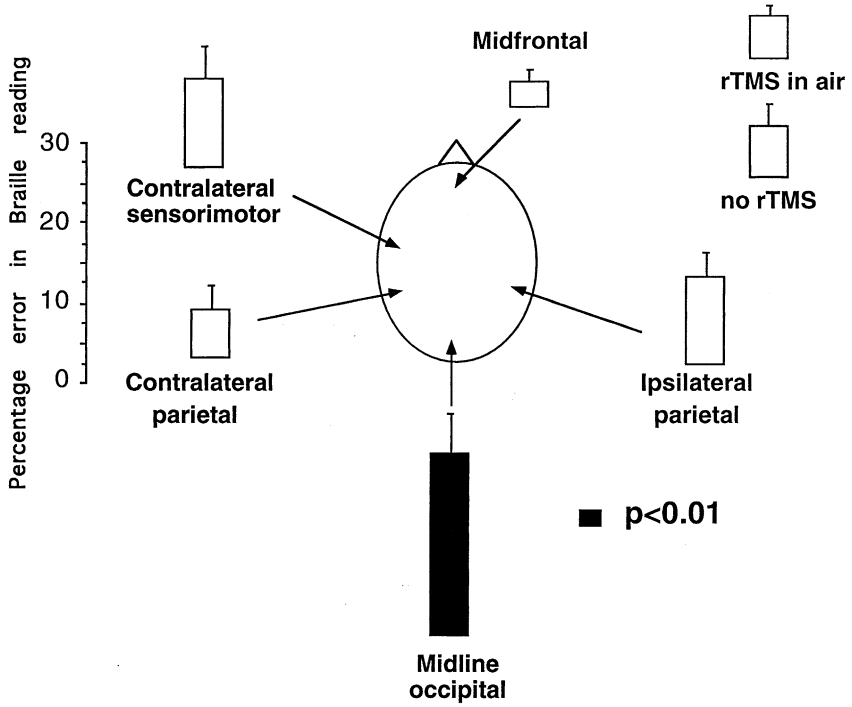

Fig. 4. Disruption of Braille reading in early blind subjects by rTMS. Four blind subjects read Braille with the right index finger while rTMS (10 Hz, 3 s duration, 110% of motor threshold) was applied to different scalp positions. The percentage error in Braille reading at each position was determined; error rates were significantly higher for the midline occipital position compared to control condition (rTMS in air). Error rates for the other scalp positions (midfrontal, ipsilateral parietal, contralateral sensorimotor and contralateral parietal) were not significantly different from the control condition. In normal subjects, occipital rTMS had no effect on a similar tactile discrimination task with the right index finger. These results suggest that the occipital cortex plays a role in Braille reading in early-blind subjects. Modified from Cohen et al. (1997).

tors, changes in membrane conductance that enhance the effects of weak or distant inputs, displacement of presynaptic elements to a more favorable site, decreased inhibitory inputs or removing inhibition from excitatory inputs (unmasking excitation) (Kaas, 1991). Among these possibilities, the evidence is strongest for removal of inhibition to excitatory synapses, which is likely due to reduced of GABAergic inhibition, in mediating short-term plastic changes.

Role of GABAergic inhibition. Several lines of evidence indicate that modulation of GABAergic inhibition plays a significant role in cortical plasticity. GABA is the most important inhibitory neurotransmitter in the brain (Jones, 1993). GABAergic neurons constitute 25–30% of the neuronal population in the motor cortex and their horizontal connections can extend up to 6 mm or more (Gilbert and Wiesel, 1992; Jones, 1993). Following application of the GABA antagonist bicuculline to the forelimb area of the motor cortex, stimulation of the adjacent vibrissa area led to forelimb movements, suggesting that GABAergic neurons are crucial to the maintenance of cortical motor representations (Jacobs and Donoghue, 1991). These changes are similar to the expansion of TMS maps of the involved muscles following transient deafferentation (Brasil-Neto et al., 1993) or peripheral nerve lesions (Merzenich et al., 1983; Donoghue et al., 1990). Deafferentation of the somatosensory (Welker et al., 1989) or visual cortex (Hendry and Jones, 1986) also led to a reduction in the number of neurons containing GABA or its synthesizing enzyme, glutamic acid decarboxylase.

Assessment of intracortical inhibition in humans. The technique of paired-TMS, with a subcortical conditioning pulse followed by a suprathreshold test pulse, can be used to test intracortical inhibition and facilitation in humans (Kujirai et al., 1993). At short interstimulus intervals (ISIs) (1–4 ms), the test pulse is inhibited by the conditioning pulse. At long ISIs (8–15 ms), the test pulse is facilitated. There is evidence that inhibition of the test MEP by the subthreshold conditioning stimulus is a cortical phenomenon. A TES test pulse, which activates mainly corticospinal axons and is less affected by cortical excitability than TMS, is not suppressed by a subthreshold conditioning TMS pulse (Kujirai et al., 1993). In addition, the subthreshold conditioning TMS pulse does not change spinal motoneuron excitability since it does not affect the H-reflex in upper- (Kujirai et al., 1993) or lower-limb (Chen et al., unpublished observations) muscles. Furthermore, cervical epidural recordings demonstrated reduction of corticospinal volleys of the test stimulus due to the conditioning stimulus (Nakamura et al., 1997). Facilitation is mediated by mechanisms separate from inhibition (Ziemann et al., 1996c) and is also likely due to cortical mechanisms,

based on H-reflex studies of the hand muscles (Ziemann et al., 1996c) and cervical epidural recordings of corticospinal volleys (Nakamura et al., 1997).

Intracortical inhibition in transient deafferentation. We applied paired-TMS to the biceps muscle during transient deafferentation induced by forearm ischemia and found reduced intracortical inhibition (Corwell et al., 1997). The TMS motor threshold remains unchanged during transient deafferentation (Brasil-Neto et al., 1993; Corwell et al., 1997). These changes may be related to reduced in GABAergic inhibition, since drugs that enhance GABAergic inhibition such as ethanol, lorazepam and vigabatrin increase intracortical inhibition but have no effect on TMS motor threshold (Ziemann et al., 1996a,b). These findings suggest that changes in GABAergic inhibition can be rapidly induced in humans.

Mechanisms for long-term changes

Plasticity changes that occur over a longer time likely involve mechanisms in addition to the unmasking of latent synapses. These may include long-term potentiation (LTP), which requires NMDA receptor activation and increased intracellular calcium concentration, and has been demonstrated in the motor cortex (Hess and Donoghue, 1994). Axonal regeneration and sprouting with alterations in synapse shape, number, size and type may also be involved (Kaas, 1991).

Mechanisms for reorganization in amputees. We studied the mechanisms for reorganization in lower-limb amputees with testing of TMS motor threshold and paired-TMS studies. Both TMS threshold and intracortical inhibition were reduced for the muscle just proximal to the amputation (Chen et al., 1997a). Therefore, it appeared that diminished intracortical inhibition, which may be related to reduced GABAergic inhibition and occurs shortly after deafferentation (Corwell et al., 1997), persists for prolonged periods after deafferentation. Changes in motor threshold apparently required longer time to develop, because the motor threshold was unchanged with transient deafferentation. The mechanisms underlying reduction in motor threshold are likely separate from those for intracortical inhibition, since the motor threshold is altered by drugs that change membrane excitability, whereas intracortical inhibition is altered by drugs that influence GABAergic mechanisms (Ziemann et al., 1996b; Chen et al., 1997b). Because the excitability of subcortical structures is unchanged, the reduction of motor threshold likely involves enhancement of cortico-cortical connections (Chen et al., 1997a). Since drugs that block voltage-gated sodium channels raise the motor threshold, one possible mechanism involves changes in sodium channels. Shifts in the voltage dependence of sodium-channel activation have been implicated in motoneuron plasticity in the spinal cord (Carp and Wolpaw, 1994; Halter et al., 1995). Other mechanisms are also possible, including LTP, axonal regeneration and formation of new synapses.

INFLUENCE OF AGE ON THE EXTENT OF PLASTIC CHANGES

Many studies have demonstrated that age is an important factor in determining the extent of plasticity changes. Injury occurring at a younger age is often associated with more extensive reorganization and better functional outcome. Several animal studies compared the reorganization following injury at different ages. Following denervation of the front paw, the reorganization of the S1 as shown by response of the 'paw cortex' to forearm stimulation was more marked in kittens (1.5–3 weeks old) than adult cats (Kalaska and Pomeranz, 1979). In cats spinalized at 2 weeks of age, a second complete map of the intact trunk and forelimb was found in the deafferented hindlimb S1, whereas in cats spinalized at 6 weeks, trunk afferents only partially activated the deafferented hindlimb area (McKinley et al., 1987). The ability to reorganize the somatotopic representation of the S1 is also age-dependent. Fetal monkeys that had median nerve transection followed by surgical repair subsequently developed an orderly representation of the reinnervated hand in the S1, similar to normal monkeys. In contrast, adult monkeys undergoing the same procedure developed a disorganized somatotopy of the hand in the S1 (Florence et al., 1996). In the motor system, neonatal and adult rats showed similar changes in M1 after forelimb amputation, with decreased stimulation threshold and enlargement of shoulder and vibrissa representations. However, the changes were more extensive in neonatal than adult rats (Donoghue and Sanes, 1988; Sanes et al., 1990).

Human studies confirmed that in children with hemiplegic cerebral palsy due to brain injury before birth or shortly after birth, the affected side had much better function compared to patients with late-occurring injuries (Carr et al., 1993). Patients who underwent hemispherectomy in early childhood also had better functions of the affected side than patients with hemispherectomy after brain maturation (Benecke et al., 1991). Similarly, while we demonstrated cross-modality plasticity with involvement of the visual cortex in Braille reading in subjects blinded early in life (Sadato et al., 1996; Cohen et al., 1997), preliminary studies showed that in subjects blinded late in life, Braille reading did not activate the visual cortex and was not interrupted by repetitive transcranial magnetic stimulation (rTMS) over the visual cortex. It appears there is no cross-modal plasticity in late-blind subjects. These studies also indicate that the developing brain is capable of a much greater degree of plasticity changes than the adult brain. There are conflicting reports regarding the extent of reorganization of congenital compared to traumatic amputees. Hall et al. (1990) found increased corticospinal excitability with TMS on the amputated side in congenital and early amputees, but not in late amputees. In contrast, Kew et al. (1994) reported increased corticospinal excitability in traumatic but not in congenital amputees. Kew et al. (1994) also reported that the magnitude of increased CBF in the deafferented sensorimotor cortex with shoulder movement was higher in traumatic than congenital amputees, and related these differences to

the absence of phantom sensation in congenital amputees.

The adult brain is also capable of a considerable degree of reorganization in animals (Merzenich et al., 1983, 1984; Pons et al., 1991) and humans (Cohen et al., 1991a; Brasil-Neto et al., 1993). In most studies, the magnitude of cortical changes was within the extent of individual thalamocortical axons (Kaas, 1991). However, there are situations where the degree of reorganization exceeded the extent of cortico-cortical connections and formation of new synapses has been suggested (Pons et al., 1991). Although the potential for regeneration is less in the adult mammalian brain compared to the neonatal brain, progenitor cells with potential to produce neurons and glia are present in the temporal lobe subventricular zone in the adult human brain (Kirschenbaum et al., 1994). In addition, axonal regeneration in the adult CNS has been demonstrated under some circumstances (David and Aguayo, 1981). The lack of regeneration generally observed in adult brain appears to be due to an environment unfavorable for regeneration, such as the absence of neurotrophic factors and the presence of inhibitors to axonal regeneration on the surface of oligodendrocytes (Schwab, 1990). It may be possible in the future to promote regeneration with neurotrophic factors, even in the adult brain.

FUNCTIONAL SIGNIFICANCE OF PLASTICITY FOLLOWING INJURY

The question of the functional significance of cortical plasticity is an important one. Does such reorganization play a functionally compensatory role? Or, are they an epiphemena with little functional relevance and may even be harmful? We will address this issue for peripheral and CNS injury separately.

Reorganization following peripheral injury

The functional role of reorganization in following peripheral injury is unclear. It is conceivable that increased cortical representation of the muscle immediately above the amputation may improve motor control of the muscle in an attempt to compensate for partial loss of a limb. Similarly, increased somatosensory representation of the stump may improve sensory perception and discrimination. However, these ideas remain speculative and in most situations, the functional significance of reorganization following peripheral lesions remains to be demonstrated. One exception may be the anastomosis of the intercostal and musculocutaneous nerves to treat cervical root avulsion. The shift in cortical representation of the biceps muscle was associated with improved control of elbow flexion and independence of biceps motor unit discharge from respiration (Mano et al., 1995). In contrast, it has been reported that the extent of sensory reorganization in amputees correlated with the degree of phantom pain (Flor et al., 1995; Knecht et al., 1996), suggesting that phantom pain may be a consequence of plasticity changes of the somatosensory cortex. Thus, it appears that plasticity changes can, in some situations, lead to functional improvement, but in other circumstances may have harmful consequences.

Reorganization following central injury

There is evidence to suggest that cross-modal plasticity resulting from visual deprivation at birth plays a functionally compensatory role. Visually deprived cats had longer vibrissae (Rauschecker et al., 1987) and performed better at sound localization (Rauschecker and Kniepert, 1994) than normal cats. In humans, hearing and sound localization may also be better in blind than in sighted subjects (Muchnik et al., 1991). In addition, the visual cortex plays a functionally important role in Braille reading in early blind subjects (Cohen et al., 1997). While these plasticity changes clearly cannot compensate for visual loss, they appear to be useful in enhancing the perceptions of other sensory modalities.

There is little doubt that recovery from stroke involves plasticity reorganization of the brain which leads to functional improvement. The challenge is to identify which of the many changes demonstrated are important in mediating recovery. One example is whether activation of the ipsilateral motor cortex with movement of the recovered hand (Weiller et al., 1993) represents involvement of ipsilateral motor pathways in stroke recovery or it merely reflects associated movement of the unaffected hand. Similar considerations apply to the importance of activation of cortical areas adjacent to the lesion. Further imaging and physiological studies involving larger numbers of patients are necessary to address these issues.

CONCLUSION

Animal and human studies in the last two decades have demonstrated that plasticity reorganization occurs in the mammalian nervous system in response to peripheral and central injuries. While plasticity changes occur at the cortical level, there is also evidence for reorganization at the subcortical, brainstem or spinal cord levels, especially in the somatosensory system in response to peripheral injury. Although the extent of plasticity changes is usually greater in the developing brain than in the adult brain, the adult brain is still capable of considerable degree of reorganization. Changes that are rapidly induced likely involve unmasking of latent synapses due to modulation of GABAergic inhibition. Additional and more extensive changes occuring in the long-term may involve changes in voltage-gated ion channels, LTP, axonal regeneration and synaptogenesis. It is important to identify which plasticity changes are beneficial and which ones may be harmful. Understanding the mechanisms of plasticity is necessary to design appropriate strategies to up- or down-regulate plasticity changes to promote recovery of function.

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