Remapping Somatosensory Cortex After Injury

Herta Flor

Department of Neuropsychology, University of Heidelberg, Central Institute of Mental Health, Mannheim, Germany

INTRODUCTION

Until recently the leading neuroscientific opinion was that the neuronal organization of the sensory and motor maps of the cortex develops early in life and remains stable throughout adulthood. Experience-dependent plasticity of the primary sensory and motor areas seemed to be limited to certain so-called critical phases in development. The results of animal experiments as well as experiments in humans with acquired neuronal damage led to a revision of this view. Plastic changes of the somatosensory and motor maps also take place in the adult central nervous system. Today it is accepted that the ability for structural and functional reorganization is a basic principle of brain function. This ability also is often referred to as neuronal or brain plasticity. "Brain plasticity refers to the adaptive capacities of the central nervous system—its ability to modify its own structural organization and functioning. It is an adaptive response to functional demand (1)."

In this chapter we present an overview of the results of animal and human studies on the reorganization of the adult somatosensory cortex related to injury. In addition to the description of functional and structural changes related to injury, we also address the potential mechanisms of these changes, their functional significance, and potential clinical applications.

ANIMAL STUDIES

Remapping of somatosensory cortex refers to the alteration of the location or size of the homuncular representation of somatosensory inputs. Although the Penfield and Boldrey (2) description established the idea of a somatosensory homunculus, current research on the anatomy of the somatosensory cortex has questioned this assumption and rather convincingly showed multiple representations of the body in different subsections of the somatosensory cortex (3,4). Thus, the discussion of reorganization must be viewed with respect to these rather complicated representations that also seem to change based on attentional factors and situational demands (5). Therefore, the somatosensory cortex must be viewed as a very flexible dynamic and adaptive system, and specific representations may be just one expression of the variety of states that may characterize somatosensory cortex. As a consequence, topographic representations are manifestations of physiologic interactions rather than anatomic constructs (6).

Experiments on lesion-induced plasticity of the adult somatosensory cortex were performed in adult monkeys in whom the afferent neuronal input was interrupted by severing a nerve or by amputating a digit (7–10). In these studies, an invasion of the representation zone of the deafferentated or amputated body part in primary somatosensory cortex by
neighboring areas was reported. For example, after the amputation of the third or both the second and third digits in owl monkeys, the representation zones of the neighboring digits and palmar zones expanded topographically into the cortical zone that formerly represented the amputated digit(s) in area 3b of the primary somatosensory cortex as revealed by microelectrode recordings. Accompanying changes in receptive field sizes showed an expansion into the deafferentated territory and the authors suggested that there might be parallel changes in sensory acuity. The changes observed in these studies were in the range of millimeters and could be explained by alterations in synaptic strength of existing connections. Pons et al. (11) reported changes of a magnitude of 1 to 2 cm in adult macaque monkeys who had been subjected to sectioning of the dorsal roots in the area C2 to T4 12 years earlier. In these monkeys, neuronal input from the face now activated the cortical zone that had previously represented the hand and arm region (Fig. 12.1). Neurons in a large section of areas 3b and 1 that had been deafferentated now responded to touch and brushing of the lower face. The question was raised to what extent this reorganizational change might be related to the growth of new connections because it could no longer be explained by alterations in synaptic strength. Changes of similar magnitude also were reported by Florence and Kaas (12) in monkeys with longstanding hand amputations.

Substantial cortical reorganization also occurs after central lesions. For example, Jain et al. (13) performed complete unilateral transection of the dorsal columns at the C3/C4 level and showed that after a period of several months the representation of the upper limb was invaded by the face representation and responded to input from the face. Jenkins and Merzenich (14) reported that small infarcts of SI led to a takeover of inputs of this zone by adjacent territory in conjunction with an enlargement of receptive fields.

**HUMAN STUDIES**

The results on adult cortical plasticity in animals were soon replicated in humans. Ramachandran, Stewart, and Rogers-Ramachandran (15) observed in three amputees that slight tactile stimuli applied with a Q-tip or strong pressure on the face led to referred sensations in the amputated (phantom) hand or arm with a point to point correspondence of the sites of referred sensation and stimulation sites in the face. They saw similarities to the findings of Pons et al. (11) and postulated

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**FIG. 12.1. I to II** —This shows two flattened maps of SI, the left showing the deafferentated zone, and the right the recording site density in one animal. Note that the face representation has expanded over the entire zone of deafferentated cortex. **III to VI**: These show receptive field data from the cortex investigated. **III to V**: These are sections of cortex in the deafferentated zone. **VI**: This is next to the deafferentated zone. Note that there are receptive fields in the chin area in the portion of cortex that normally represents the arm and hand. (From: Pons TP, Garraghty PE, Ommaya AK, et al. Massive cortical reorganization after sensory deafferentation in adult macaques. *Science* 1991; 252:1857–1860, with permission.)
that the phenomenon of referred phantom sensation was a perceptual correlate of the reorganization that occurs subsequent to amputation and called it “facial remapping.” Elbert et al. (16,17) used neuromagnetic source imaging (a combination of magnetoencephalographic recordings and magnetic resonance imaging) to determine the homuncular organization of the primary somatosensory cortex in upper extremity amputees. In all amputees a shift of the neuronal activity that was elicited by facial stimulation into the area that formerly represented the now-amputated hand and arm in primary somatosensory cortex was observed. The authors used the Euclidean distance between the hand and mouth representation of the intact side and compared it to the amputated side by mirroring the representation of the intact hand onto the other hemisphere (to replace the representation of the amputated hand, assuming symmetric representation on both hemispheres). In some cases this shift of the mouth toward the hand region spanned a distance of several centimeters.

Similar changes were also reported by Kew et al. (18) who used transcranial magnetic stimulation and positron emission tomography in a sample of arm amputees. Plastic alterations also occur in motor cortex probably owing to its close association with somatosensory cortex (19). Mogilner et al. (20) used magnetic source imaging to follow the changes that occurred subsequent to the separation of a syndactyly (“webbed hand”). Whereas the hand representation was “smeared” before surgery, after surgery the separation of the fingers was mirrored in separate representation of the individual fingers in primary somatosensory cortex.

This change in cortical organization is most likely only present when the deafferentation occurs after the completion of cortical development. Persons who lost a limb in the prenatal phase and very young child amputees did not report phantom sensation or phantom limb pain in two studies (21,22). In addition, they showed no reorganization of somatosensory cortex. However, contrary to these results Brugger et al. (23) reported phantom sensation and reorganization in a sample of subjects with congenital aplasias in accordance with reports on phantom sensations in congenital amputees by Melzack (24). The role of early experience and learning in injury-related plasticity thus needs to be further clarified.

Transient deafferentation achieved by nerve blocks or regional anesthesia was studied in humans. For example, Rossini et al. (25) showed that somatosensory evoked magnetic fields can be influenced by transient ischamic deafferentation. A shift of the representation of the stimulated finger toward the representation of the deafferented finger was observed. Attentional factors were found to modulate the extent of transient deafferentation (26).

FUNCTIONAL SIGNIFICANCE

Surprisingly, the reorganization observed in amputees was not associated with the presence of topographic referred sensations as postulated by Ramachandran et al. (15). In several subsequent studies less than 20% of the amputees were found to show topographic referred sensation, whereas a much larger percentage (60% to 80%) of the amputees was significantly reorganized (27,28). Rather, phantom limb pain was soon identified as a perceptual correlate of cortical reorganization. A larger shift of neighboring representation zones into the zone that formerly represented the amputated limb was associated with more phantom limb pain (21,22,27–31). Whereas amputees with phantom limb pain showed a mean reorganization of 1.5 cm, the pain-free amputees revealed less than 4 mm reorganization (29) (Fig. 12.2).

As noted, nonpainful phantom sensations have consistently not been related to changes in the somatotopy of somatosensory cortex (28). Upper extremity amputees who experienced nonpainful phantoms when stimulated at the finger or the mouth showed increased activation levels in primary somatosensory cortex, posterior parietal cortex and reduced activation in ipsilateral secondary somatosen-
sory cortex (32) rather than a change in ho-
muncular organization. A similar reduction in
SII activity was also reported by Hari et al.
(33) when a supernumerary limb was present
in a patient who had suffered brain damage.
Thus, phantom limb pain seems to be associ-
ated with changes in primary somatosensory
cortex, whereas nonpainful phantom phe-
nomena seem to be related to alterations in
other brain areas such as the posterior parietal
cortex.

Anesthesia of the brachial plexus in upper
limb amputees suffering from phantom limb
pain revealed that about half of the amputees
achieved a temporary reduction of phantom
limb pain whereas the other half continued to
display phantom limb pain (30). The neuro-
electric source analysis of activity in primary
somatosensory cortex revealed that the pain-
free amputees no longer showed cortical reor-
ganization; that is, their lip representation had
shifted back to the location where the lip rep-
resentation of the intact side was located. The
amputees without a change in phantom limb
pain showed a small increase in reorganiza-
tion; that is, the lip representation shifted even

FIG. 12.2. Representation in primary somatosensory cortex of the mouth and two digits in upper ex-
tremity amputees with and without phantom limb pain. Note how the mouth representation of the am-
putation side has shifted into the hand region in the amputees with pain.
further into the region of the hand and arm. These data confirmed the hypothesis of a close association of phantom limb pain and changes in the map of the somatosensory cortex.

Similar alterations were found in patients with chronic low back pain (34). Electric stimulation of the back and finger resulted in enhanced activity in primary somatosensory cortex in response to the back but not the finger stimulation in the chronic back pain group as compared to healthy controls and subchronic patients. When the magnetic fields related to this stimulation were localized a shift and expansion of the back representation toward the leg area was found in the chronic group that was the larger the more chronic the pain has become. This type of “somatosensory pain memory” was assumed to contribute to the hyperalgesia and allodynia that is often found in states of chronic pain (35).

Flor (36) suggested a model of phantom limb pain that assigns a special role to cortical reorganization (Fig. 12.3). It has long been known that the primary somatosensory cortex is involved in the processing of pain and that it may be important for the sensory-discriminative aspects of the pain experience. There have been reports that phantom limb pain was abolished after the surgical removal of portions of the primary somatosensory cortex and that stimulation of somatosensory cortex evoked phantom limb pain. The model postulates that longstanding or intense acute pain in the limb prior to or during amputation may lead to the establishment of a somatosensory pain memory (37). These pain memories do not have to be explicit and thus open to conscious perception by the patient but can be implicit and may merely consist of a physiologic alteration of the somatosensory cortex. If such an implicit pain memory has been established with an important neural correlate in primary somatosensory cortex, subsequent deafferentation and an invasion of the amputation zone by neighboring input may activate preferentially cortical neurons coding for pain. Because the cortical area coding input from the periphery seems to stay assigned to the original zone of input the activation in the cortical zone representing the amputated limb is referred to this limb and the activation is interpreted as phantom sensation and phantom limb pain.

MECHANISMS

In the studies on reorganization of somatosensory cortex several phases of reorganization seem to be present. A first, very fast phase with an expansion of neighboring areas into the representation zone of the deafferentated area without necessarily completely filling this region was observed. Next was an intermediate phase that extended over weeks with a consolidation and new formation of the topographic organization and finally a third phase with a continued expansion and use-dependent changes (38). Phantom limb pain and phantom sensations can be present already in the very early stages of reorganization after amputation (39). In addition, transient alterations of somatosensory input such as the application of painful stimulation can also lead to immediate changes in the somatosensory map (40).
The original interpretations of the changes in the median-nerve sectioned monkeys were based on the assumption that week and ineffective synapses in the fringes of overlapping thalamocortical axon arbors would be potentiated. Since the discovery of massive reorganization in somatosensory cortex a number of mechanisms have been viewed as basic for these reorganizational processes. However, it is so far not clear which of these mechanisms are decisive, if they are different in the early and late stages of cortical plasticity, and if they differ between lesion- and stimulation-induced plasticity. In addition, there have been extensive discussions about the site of remapping, specifically, to what extent there is genuine cortical plasticity and to what extent cortical changes merely reflect alterations at lower levels of the neuraxis (41).

Any alteration of the pattern of input from a sensory surface immediately leads to map changes in the brain regions activated by these inputs. These map changes, however, are far from straightforward because normally an intricate pattern of inhibitory and excitatory circuits is present. The alteration of the balance of excitatory and inhibitory interactions has been described as unmasking of normally silent connections (42). Unmasking seems to depend on GABAergic mechanisms (43). Arckens et al. (44) showed with respect to the visual cortex that a GABA decrease also may be related to changes in synaptic efficiency and thus still be present long after unmasking has occurred.

The activity-dependent upregulation of glutamate at the NMDA receptor is another important mechanism of reorganization. Garraghty and Muja (45) showed that an NMDA receptor blockade after the sectioning of the median nerve led to substantially less reorganization than is normally observed. The small number of neurons that was responsive to skin stimulation was thought to be active because of unmasking that is not NMDA receptor dependent. Myers et al. (46) showed that although the later stage of reorganization is NMDA receptor dependent, the maintenance of reorganization depends on the activation of AMPA receptors.

Another mechanism that has been discussed is sprouting of new connections on several levels of the central nervous system. In monkeys with hand and forearm amputations, Florence and Kaas (12) showed that afferents from the remaining forelimb extended into the hand areas in both the dorsal horn and cuneate nucleus in the brainstem; thus suggesting that sprouting may occur on lower levels. The sprouting of new intracortical connections was shown by Florence, Taub, and Kaas (47) in monkeys subsequent to amputation or bone fractures. Injection of tracers revealed normal thalamocortical connections in area 1 but sprouting in the lateral connections in areas 3b and 1, suggesting cortical rather than thalamic changes (Fig. 12.4). Jones and Pons (48), however, examined macaque monkeys with longstanding dorsal rhizotomies and reported extensive transneuronal atrophy at the thalamic level. Merzenich (49) suggested that the level of deafferentation might explain these divergent findings because deafferentation at the spinal level is accompanied by neuronal degeneration in the dorsal root, whereas this is not the case in peripheral deafferentation. In this context the results of Ergenzinger et al. (50) are important; they showed that acute and chronic suppression of activity in SI can result in massive thalamic changes. This is related to the anatomic fact that the efferent connections from cortex are about tenfold stronger than those to cortex if one considers thalamocortical connections.

Changes in sensory maps as a consequence of deafferentation can occur at the cortical or subcortical level. Reorganization also has been observed on the thalamic level. For example, Garraghty and Kaas (51) recorded from the ventroposterior lateral nucleus of the thalamus of deafferentated monkeys and found extensive reorganization. Local anesthesia-induced reorganization in the ventral posterior medial nucleus (52) was observed as well. In monkeys with longstanding dorsal rhizotomies, Rausell et al. (53) found a selective degeneration of non-nociceptive pathways and increased activity of nociceptive cells in the thalamus. In a thalamic stimula-
FIG. 12.4. Summary reconstruction of the hand representation in area 3b and a partial representation of the hand in area 1 based on electrophysiologic recordings using a retrograde tracer. On the left side the normal connections are shown, on the right side connections in an amputated monkey are displayed. (From: Florence SL, Taub HB, Kaas JH. Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. Science 1998;282:1117-1120, with permission.)

A change in synaptic connections related to Hebbian learning and long-term potentiation (LTP) is another equally important mechanism that may be involved in reorganizational changes (55). Long-term potentiation has been shown in the hippocampus mainly. In the cortex it is more complex because of the less well segregated and classified cell types and afferent pathways (42).

IMPLICATIONS FOR REHABILITATION

Based on the findings from neuroelectric and neuromagnetic source imaging, it is possible that changes in cortical reorganization might influence phantom limb pain. Animal work on stimulation-induced plasticity suggests that extensive behaviorally relevant (but not passive) stimulation of a body part leads to an expansion of its representation zone (56). Thus, the use of a myoelectric prosthesis might be one method to influence phantom limb pain. It was shown that intensive use of a myoelectric prosthesis was positively correlated with both reduced phantom limb pain and reduced cortical reorganization (19). When cortical reorganization was partialled out, the relationship between prosthesis use and reduced phantom limb pain was no longer significant, suggesting that cortical reorganization mediates this relationship. An alternative approach in patients where prosthesis use is not viable is the application of behaviorally relevant stimulation. A 2-week training that consisted of a discrimination training of electric stimuli to the stump for 2 hours per day led to significant improvements in phantom limb pain and a significant reversal of cortical reorganization. A control group of patients who received standard medical treatment and
general psychologic counseling in this time period did not show similar changes in cortical reorganization and phantom limb pain (57) (Fig. 12.5). The basic idea of the treatment was to provide input into the amputation zone and thus undo the reorganizational changes that occurred subsequent to the amputation. Ramachandran (58), who used a virtual reality box to train patients to move the phantom and reduce phantom limb pain, described another behaviorally oriented approach. A mirror was placed in a box and the patient inserted both his or her intact arm and the stump. The patient was then asked to look at the mirror image of the intact arm, which was perceived as an intact hand where the phantom used to be. The patient was then asked to make symmetric movements with both hands, thus suggesting real movement from the lost arm to the brain. This procedure seems to reestablish control over the phantom and reduce phantom limb pain in some patients.

Pharmacologic interventions also might be useful in the alteration of cortical plasticity and the amelioration of phantom limb pain related to central changes. Animal studies have shown that both spinal sensitization and cortical reorganization can be prevented or reversed by the use of NMDA receptor antagonists (42,59). Reorganization also was found to be related to reduced GABAergic activity and increased cholinergic activity. Thus, these substances should be beneficial in the treatment of phantom limb pain. However, studies in patients are scarce and the data are controversial. For example, whereas some studies reported a positive effect of the NMDA receptor antagonist ketamine on phantom limb pain, others found no effects of the NMDA receptor antagonist memantine on chronic phantom pain phenomena (60).

A recent study used the NMDA receptor antagonist memantine versus placebo in addi-
tion to brachial plexus anesthesia in patients undergoing traumatic amputations of individual fingers or a hand (61). It was found that memantine significantly reduced the incidence of phantom limb pain 1 year after the surgery, whereas placebo failed to show a similar effect (Fig. 12.6). In this study, very low levels of cortical reorganization and phantom limb pain were observed as well.

**SUMMARY**

The results reported here show convincingly that the adult somatosensory cortex alters its maps subsequent to injury. Studies with amputees and chronic pain patients have shown that pain may be a important perceptual correlate of the changes that were observed in primary somatosensory cortex. These results also have led to new approaches to rehabilitation. Both pharmacologic and behavioral interventions designed to alter cortical reorganization were found to not only alter the organization of primary somatosensory cortex but also maladaptive perceptual phenomena that accompany these changes.

**ACKNOWLEDGMENTS**

This research was supported by the Deutsche Forschungsgemeinschaft and the Max Planck Research Award for International Cooperation.

**REFERENCES**


