Reorganization of Somatosensory Cortex After Nerve and Spinal Cord Injury

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Somatotopic maps in the mature brain reorganize in response to deafferentation by peripheral nerve cut, amputations, or spinal lesions. Mechanisms underlying these changes may range from altered tonic inhibition and synaptic efficacy to neuronal sprouting. An understanding of these mechanisms could guide interventions that potentiate recovery from such injuries.

Until recently, most neuroscientists believed that the adult brain is hard wired and largely incapable of reorganization. The only areas of the brain where some reorganization might occur would be those involved in learning and skill acquisition. However, over the past two decades, it has been conclusively established that even primary sensory areas of the brain are capable of reorganization in response to injuries or changes in patterns of peripheral stimulation. In this review, we focus on the changes that take place in the somatosensory pathway in response to injuries to peripheral nerves and spinal cord afferents in monkeys. Data from other mammalian species are also considered, and we correlate the animal work with available results from humans. Much of the research on cortical plasticity has involved New World owl and squirrel monkeys, which have most of the primary somatosensory cortex (area 3b) exposed on the surface (Fig. 1). This technical advantage allows for reliability, accuracy, and thoroughness in the multiunit mapping experiments. Old World macaque monkeys have also been studied in great detail, since they have a closer evolutionary relationship with humans. In addition, if similar results are obtained from more than one species, it can be reasonably concluded that the results reflect fundamental properties of the primate nervous system, not just peculiar features of a particular species. The results can then be more confidently generalized to humans.

Normal organization of somatosensory areas in monkeys

Before a consideration of plastic changes that take place in the somatosensory regions of the brain in reaction to injuries, it is useful to describe the normal organization of these areas.

As the information travels from the receptors in the skin to the cortex, near-neighbor relationships of the periphery are maintained. This results in maps of the body surface in processing stations of the somatosensory system in the brain stem (trigeminal, cuneate, and gracile nuclei), thalamus [ventroposterior nucleus (VP)], and cortex (areas 3b, 1, 3a, 2, and other areas) (Fig. 2). The map of the body surface in primary somatosensory cortex (3b) has been revealed in detail in a number of primate species by recording neuronal responses to peripheral stimulation using microelectrodes. The normal map has a number of characteristic features. There is an orderly somatotopic representation, from lateral to medial, of face, hand, arm, trunk, leg, and foot. The somatotopy exists in even finer detail, so that, within the hand representation, digit 1 (thumb) is represented laterally and digit 5 is represented medially. Most of the area of the hand representation is occupied by the representation of the glabrous surface of the hand. Dorsal or hairy skin is represented in small islands in the hand region. When two different somatosensory areas abut each other, they have mirror image representations of body parts. Thus, in the hand representation in area 3b, digit tips are represented rostrally and the palm is represented caudally, and, in area 1, which is immediately caudal to area 3b, digit tips are represented caudally and the palm is represented rostrally. These consistent features of body representation in normal monkeys allow one to reliably determine plastic changes that might take place as a result of injuries, despite not knowing the normal preinjury map in the same animal.

Somatotopic organization has also been mapped in the VP of the thalamus and in the brain stem nuclei (8). However, these nuclei lie much deeper in the brain, where they are relatively inaccessible. In addition, unlike two-dimensional representations in the cortex, maps in these nuclei are three dimensional, which makes it technically more difficult to map these structures. Therefore, most of the plasticity stud-
ies have examined the cortex.

On the basis of the nature of the changes that take place after sensory deprivation and their possible mechanisms, it is possible to divide the time course of these changes into three, perhaps not mutually exclusive, categories. First, there are immediate changes that take place within minutes to hours of the peripheral deprivation. Second, there are short-term changes that occur within days to weeks. Third, there are long-term changes that take months to manifest. The early changes may influence the outcome of later changes.

Brain reorganization following peripheral nerve injuries

In the earliest studies that conclusively demonstrated that the adult somatosensory cortex is capable of reorganization, the brain was deprived of its normal inputs by cutting the median nerve to the hand in owl and squirrel monkeys (9). The median nerve innervates the radial (thumeward) half of the glabrous hand. If this nerve is cut and ligated to prevent regeneration, the lateral half of the hand area in the cortex becomes deprived of all the normal glabrous inputs (see Fig. 3A). If the cortex is mapped immediately after such a deprivation, the former median nerve territory is not completely unresponsive. Parts of the median nerve territory are reactivated by expanded representations of the radial nerve inputs that represent the hairy skin on the back of the hand (9). Over a period of 3 wk, the remaining silent cortex becomes completely reactivated, largely by radial nerve inputs (Fig. 3B). Initially, receptive fields in the reorganized cortex are large, with little discernible somatotopy. Over time, the receptive fields become smaller and a somatotopy similar to preinjury is established, except that the receptive fields are on the back of the hand rather than on the glabrous skin. In addition, there is some expansion of the ulnar nerve inputs, which represent the remaining half of the glabrous hand, into adjacent cortical territory, particularly in the palmar area (Fig. 3B).

If both median and ulnar nerves to the hand are transected, the entire hand representation in cortex is deprived of its glabrous inputs. Over a period of time, this large region of deprived cortex becomes responsive to stimulation of the back of the hand (Fig. 3C). However, if radial nerve section is combined with either median or ulnar nerve transection, large tracts of the cortex remain silent for a period of at least 11 mo and perhaps permanently (Fig. 3D). Thus the extent of cortical reactivation following nerve transections seems to depend on the innervation pattern of the nerves rather than on the extent of deprived skin or the central cortical territory. Similarly, in rats, transection of the sciatic nerve, which innervates parts of the hind foot, leads to only a limited expansion of the remaining saphenous territory in the cortex. Large parts of the former sciatic cortex remain...
If a nerve is cut but allowed to regenerate by suturing the cut ends together, the regenerated nerve is able to reactivate much of its original cortical territory in both owl and macaque monkeys. However, the somatotopic organization remains highly abnormal (3). Many neurons in the reorganized cortex have multiple receptive fields such that neurons at the same cortical site respond to stimulation of nonadjacent skin areas. In addition, many parts of the skin innervated by the regenerated nerve have split representations. That is, the same or adjacent regions of the skin are represented in noncontiguous chunks of cortex. The normal somatotopy is never reestablished. Both multiple receptive fields and split representations are seldom seen in normal animals. In contrast, if a nerve is crushed, instead of cut, and allowed to regenerate, the axons regenerate into their original fascicles, and a normal pattern of peripheral innervation is reestablished. In owl monkeys, the crushed and then regenerated median nerve is not only able to recapture all of its original territory but a normal somatotopy is also reestablished in area 3b (15). In adult humans with nerve section and nerve repair, sensory mislocalizations seem to persist permanently after regeneration of the nerve, which indicates that the errors in regeneration are not corrected in the brain. Similarly, when a flap of skin is transferred along with its associated nerves from a digit to thumb to restore sensation to the thumb, mislocalization persists for months (11). This procedure creates a situation that is analogous to the nerve regeneration errors. Magnetoencephalography in these patients revealed that both the finger and the skin flap on the thumb are represented in the same region in the cortex, unlike the separate representation of the thumb and the digit in normal subjects, an equivalent of the multiple receptive fields observed in monkeys with regenerated nerves.

Cortical reorganizations of a very large scale can take place after more massive deafferentations. In macaque monkeys studied 12 yr or more after complete deafferentation of inputs from the arm by section of dorsal roots, the deprived hand and arm cortex are activated by inputs from the chin and jaw, an expansion of more than 10 mm (13). In contrast, cutting all the nerves to the forelimb does not result in a complete reactivation of the deprived somatosensory cortex in cats for at least up to 1 yr (2). These differences may occur because the two types of deafferentations are not identical, even though they produce similar extents of deprived cortex. Transection of the nerves results in the degeneration of processes of neurons distal to the cell bodies in the dorsal root ganglia. The proximal processes of many of these neurons would remain intact. In animals in which the dorsal roots are sectioned, the proximal processes of neurons would degenerate, resulting in vacated synaptic space, thereby creating more favorable conditions for the growth of remaining axons in the spinal cord and cuneate nucleus.

The changes in the somatotopic organizations seen after peripheral nerve injuries are not limited to the cortex. The VP of the thalamus in squirrel monkeys reorganizes in a manner similar to cortex after median and ulnar nerve cut and ligation (5). The hand subnucleus of the VP becomes responsive to the back of the hand, just as in the cortex. At the medullary level, transection of the dorsal roots caudal to L4 leads to immediate expansion of the representation of the ventral trunk in the nucleus gracilis of cats. These changes become more marked after a longer survival period of 8 mo (1). In these longer-surviving cats, cells in the dorsal horn of the spinal cord at L6 and L7 levels respond to the stimulation of the ventral trunk, unlike in normal animals. Similar reorganizations have been seen in a wide range of species. Thus plastic changes are also seen in
the thalamus, medullary nuclei, and spinal cord.

**Brain reorganization following amputations**

Amputation of a distal extremity differs from a sensory nerve cut, since all of the afferent and efferent nerves are severed. In addition, large sheets of receptors in the skin are permanently lost. The pattern of cortical reorganization after amputation of one or more digits in owl monkeys (10) is similar to that seen after transection of either ulnar or median nerve combined with radial nerve cut. There is some expansion of adjacent inputs into the denervated cortex, but parts of the cortex may remain unresponsive after many weeks of recovery. However, if larger areas of the cortex have been deprived by the amputation of the hand or arm, the cortical representation of the remaining arm expands into the hand representation (4). In addition, there is limited expansion of the face inputs into the hand cortex. Finally, there are varying amounts of cortex, in both owl monkeys and macaque monkeys, that respond only to high threshold cutaneous stimulation even years after the therapeutic amputation of the hand or arm. Responses to the stimulation of face in the deprived hand cortex have also been seen in brain imaging studies of humans with arm or hand amputations. This type of reorganization may produce highly abnormal sensory experiences, such as the perception of a phantom of the missing arm when the face or the stump is stimulated.

**Plasticity following spinal cord injury**

Most of the information used in fine tactile discriminations in primates travels in the dorsal columns of the spinal cord. However, the behavioral and physiological deficits after transection of the dorsal column have been variably reported, ranging from mild and transient to significant. Thus much uncertainty remains. Results of experiments involving dorsal column sections can be difficult to interpret for several reasons. First, unlike the nerve section experiments, it is more difficult to consistently achieve complete section of the dorsal columns without damaging pathways in the adjacent lateral and ventral tracts and the spinal gray. Second, it is difficult to determine the extent and source of any remaining fibers by a simple histological examination of sections of the postmortem spinal cord, particularly if the remaining fibers are few. Third, the possibility that plastic changes potentiate the remaining inputs has not been considered in many studies. Finally, it is important to precisely relate recording sites in the reorganized cortex to normal somatotopy, which is more difficult if the areas of deactivation and abnormal response...
properties are extensive. In a series of experiments on cortical plasticity after unilateral dorsal column section at cervical (C3/C4) levels in owl monkeys, we tried to circumvent these problems (7). To evaluate the effectiveness of the lesions, we injected transganglionic tracers at multiple sites in the skin of the hand and looked for transported label in the brain stem cuneate nucleus. The presence of any label in the cuneate nucleus indicated that the dorsal column section was incomplete. By relating the location of the transported label to the normal somatotopy in the cuneate nucleus, we could also determine the exact source of the remaining afferents. In addition, we were able to precisely relate recording sites to the normal isomorph of the body surface in area 3b, which is revealed by staining the sections of flattened cortex for myelin. This isomorph reveals the preselection organization of cortex. We found that, immediately after a complete high-cervical section of the dorsal columns, the hand portion of area 3b becomes completely unresponsive to peripheral stimulation, and it remains so for at least 3 wk (Fig. 4B). In the case of an incomplete dorsal column section, the remaining inputs initially activate neurons in their normal expected cortical territory (Fig. 4D), but, by 5 wk, they expand to activate the deafferented area of the hand cortex (Fig. 4E). Neurons in the reorganized parts of cortex have large receptive fields and abnormal response properties. After a longer survival period of 6 mo or more, a partial or complete dorsal column section results in expansion of inputs from face into the former hand territory (Fig. 4, C and F). Eventually, all of the hand and arm cortices are activated by stimulation of the face. In addition, there is some lateralward expansion of the arm inputs into the hand region. Similar reorganizations are seen in somatosensory area 3a, which lies rostral to area 3b and has type 1 muscle afferents as the predominant source of activation. The changes in area 3a have a faster time course. Expansion of face inputs into the adjacent hand area after spinal cord injuries may be the cause of phantom sensations, similar to those seen after amputations.

Mechanisms of cortical reorganization

Reorganizations in the brain may involve a number of mechanisms that result in the observed sequence of changes. These mechanisms may operate at one or more levels of processing in the somatosensory pathway. 

Disinhibition of suppressed inputs. The normal spread of the afferent terminals is larger than what is reflected in the physiologically determined excitatory receptive fields. The expression of latent inputs is inhibited at least partly by the inhibitory γ-aminobutyric acid (GABA)ergic or glycinegic interneurons. Deafferentation leads to the immediate expression of subthreshold inputs due to release of inhibition resulting from lack of excitatory inputs to the inhibitory cells (e.g., Ref. 1). Over longer time periods, reduced activity levels could lead to a reduced expression of inhibitory transmitters. Experimental data appear to support this hypothesis. A decrease in immunostaining for GABA is observed 2 mo after median and ulnar nerve transection and ligation in squirrel monkeys (6). Similarly, decreases in GABA receptor levels in the cortex and glutamic acid decarboxylase levels of VP of the thalamus have been observed in rats after peripheral deprivation. Thus the decrease in inhibition is not restricted to cortex, and disinhibition could operate at multiple levels.

Potentiation of previously ineffective inputs. According to the Hebbian hypothesis, two different inputs to a neuron with discharges that are coincident in time increase in synaptic strength, whereas discorrelated inputs weaken. A similar mechanism operating during development presumably dictates the selective pruning and final shape of the termination zone of geniculocortical arbors in the visual cortex. This leads to ocular dominance columns in the primary visual cortex that have inputs exclusively from one or the other eye. Similarly, the exuberant afferents on muscle fibers are retracted during development as a result of discorrelated activity such that the single muscle fiber is eventually innervated by arbors of only a single axon. Evidence indicates that the N-methyl-D-aspartate (NMDA)-type glutamate receptors play a role as coincidence detectors in strengthening of the synapse by a mechanism termed long-term potentiation (LTP). In the adult nervous system, similar mechanisms could lead to the weakening of synapses that are not correlated in time, even though these synapses are physically extant. These weak connections may not be expressed at a sufficient strength to activate the postsynaptic neuron. However, if the normal dominant inputs are removed by deafferentation, the weaker and previously latent synapses could become strengthened over time by LTP-like mechanisms, stabilizing and strengthening the latent inputs on the basis of the new activation patterns. Such a mechanism could operate at a single-neuron level as originally postulated by Hebb or at the group level as hypothesized by Edelman and colleagues (12). Experimentally, it has been shown that, if NMDA receptors are blocked after peripheral deafferentation, certain plastic changes fail to occur.

“Deafferentation leads to the immediate expression of subthreshold inputs…”
Growth of dendritic or axonal arbors. Long-term deafferentations may result in growth of arbors by regenerative or collateral sprouting. Afferents in the spinal cord or the cuneate nucleus have an abnormally large termination field after a nerve crush or amputation (4), which is indicative of new growth. A number of reports show that there is an upregulation of growth-associated molecules like GAP-43 in the central terminals of the dorsal root ganglion cells after peripheral axotomy. High-affinity neurotrophin receptors like trkA and trkB are upregulated in spinal cord dorsal column glial cells after dorsal root section, and there is an increase in the transport of ciliary neurotrophic factor after peripheral axotomy. Thus levels of a number of molecules that may mediate growth of processes are altered in the spinal cord by deafferentations in adult animals. Certain neurotrophins, like brain-derived neurotrophic factor and nerve growth factor, have been shown to affect somatotopy in the adult rat cortex.

Molecular mechanisms of plasticity. Aside from the examples given above, very few molecular correlates of neural plasticity are known. The estimated number of candidate genes that may be involved in neural plasticity may run well over 1,000. Some of the molecules that have been shown to be upregulated following peripheral nerve injuries include fos, an immediate early gene, and pp60src, a tyrosine kinase, a class of molecules that act like molecular switches. The exact role of these molecules in plasticity has not been determined. Considerable work will be needed to unravel the cascades of molecular events that mediate the reorganizations in adult brains.

Sites of brain plasticity

Although the cortex is the most extensively studied site of neural plasticity, this can be attributed to technical advantages rather than just the theoretical focus. The cortex has a two-dimensional representation of the body surface that is easy to expose and map. Few experimenters have mapped thalamic and brain stem nuclei to study plastic changes. Nevertheless, as described above, changes similar to those in the cortex have been demonstrated in subcortical structures. Any changes in the neuronal receptive fields that take place in a subcortical relay structure presumably would be reflected in higher processing areas even without any changes in the connections of thalamocortical neurons. Certain limited expansions of inputs could be the result of the expression of previously latent inputs at one or more levels of processing. Two examples are the limited expansion of the ulnar nerve inputs into the adjacent denervated cortical territory that is seen after median nerve cut and partial to complete filling in of the denervated cortex that occurs after digit amputation. Because certain manipulations that result in large areas of deprived cortex are followed by a complete reactivation (median + ulnar nerve section), whereas a smaller zone of deprived cortex (median + radial nerve section) may remain unresponsive even after long survival times (see Fig. 3), it is unlikely that the strengthening of unexpressed inputs in the cortex is exclusively responsible for this type of extensive reorganization. A likely site for these changes is in the cuneate nucleus of the brain stem (5), where inputs from radial and median or ulnar nerves terminate in close vicinity. Disinhibition or strengthening of the synapses in the cuneate nucleus could result in the rapid expansion of the radial nerve inputs into median or ulnar nerve territories in cortex.

Other expansions of even larger scale, for example, the expansion of the face representation into the hand cortex following dorsal root section or dorsal column section, are beyond the range of spread of afferents or intrinsic connections in cortex, thalamus, or brain stem. These large-scale changes would require considerable growth of the axon arbors if mediated in the cortex. The same changes could occur after a more limited growth of the arbors of face afferents in the trigeminal nucleus into the neighboring cuneate nucleus (4), since the map of the body at the medullary level is much smaller than in cortex. However, it remains to be directly established whether brain stem nuclei are indeed the site of these plastic changes in the brain. Peripheral sprouting of the intact nerves into the denervated skin is limited and does not contribute to the plastic changes seen in the brain. Even after long recoveries following the nerve transection and ligation and complete filling in of the denervated cortical territory, no receptive fields are seen on the denervated skin.

Although the reorganizations in the adult brain are now better understood, much remains to be learned about the mechanisms that underlie these changes. A more detailed understanding of the mechanisms of such changes and conditions under which they are expressed would help in designing interventions to treat human nervous system injuries to promote the recovery of function and prevent undesirable outcomes such as phantom sensations.

References

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