15 The Reorganization of Sensory and Motor Maps after Injury in Adult Mammals

JON H. KAAS

ABSTRACT Sensory and motor maps in the brains of adult mammals are highly plastic. The mutability of the topographic structures of these maps has been most convincingly demonstrated in the larger, two-dimensional maps of sensory surfaces in primary sensory cortex after long-standing deactivations of part of the receptor sheet. More limited modifications of cortical maps have been demonstrated after changes in experience and learning. In addition, convincing changes in subcortical maps have been demonstrated in the thalamus and brain stem, suggesting that all levels of sensory systems are modifiable, even in the mature brain. Changes in maps have been demonstrated in a range of mammalian species and in the somatosensory, visual, auditory, and motor systems. Some alterations are instantaneous, reflecting adjustments in dynamic systems. Others emerge over minutes to weeks as a result of synaptic modifications, the play of neuromodulating systems, and the regulation of the neurotransmitters. In instances of massive deafferentations, such as after the loss of a limb, major reactivations of cortical maps occur, but over longer times of months. These reactivations appear to depend, in part, on the growth of new connections. These massive reactivations lead to misperceptions referred to the missing sensory surface. Rearrangements of sensory and motor maps in the mature brain may be responsible for improvements in sensorimotor skills with practice, useful adjustment to sensory loss and change, and recoveries from central nervous system damage, as well as misperceptions and malfunctions. A fuller understanding of the mechanisms of adult plasticity might lead to improved clinical treatments and the potentiation of favorable outcomes.

One of the major surprises to emerge from research on sensory systems over the last 20 years is that the internal structures of maps of sensory surfaces in the brain are extremely mutable, even in adult mammals. The developing brain was already known to be highly plastic, since the course of development could be greatly altered by injury to part of the pathway or by sensory deprivation. In contrast, some of the same manipulations seemed to have little effect on the mature brain or even brains at later stages of development. In addition, reliable sensory perception would appear to depend on a system that is rather stable in organization. Therefore, the organization of much of the mature brain has been considered to be fixed by the end of development. Yet, some capacity for reorganization in sensory-perceptual systems would seem necessary to account for the learning of sensorimotor skills, adjustments to changes in sensory inputs, and the considerable recoveries that often occur after focal brain damage. We now know that the details of cortical representations are dynamically maintained, that changes in sensory inputs and the significance of sensory inputs can alter response properties of neurons and the structure of sensory maps over short to long time courses, and that after injuries major changes in sensory maps are possible. Some alterations are of such extent that they can only be explained by the growth of new connections. The evidence for such flexibility in brain organization leads to some obvious questions. For instance, how do such changes occur? Are they useful or harmful, and, either way, how can we control them? And, are all parts of the cortex, or brain, equally flexible, or do early and higher-order fields differ? While we have only partial answers to these and related questions, the usefulness of answering them is clear. But it is important to recognize that even after 20 or more years of intensive research, we are at the early stages of understanding the extent and nature of plasticity in the adult brain.

One of the current limits on our understanding is that only a few regions of the brain have been extensively studied. Many of the studies have been of the mutability of the hand map in primary somatosensory cortex of monkeys. A concentration of efforts on this cortex might seem strange, until one considers the technical advantages that this cortex offers. First, one needs a convincing way of demonstrating brain changes. The primary somatosensory representation is extremely precise and orderly, and the portion representing the hand in primates is rather large. The representation is two-dimensional, in

JON H. KAAS Department of Psychology, Vanderbilt University, Nashville, Tenn.

contrast to the more complex, three-dimensional, smaller subcortical representations, and the hand region of primary somatosensory cortex, at least in some primates, is exposed on the surface of the brain. These advantages allow alterations in cortex to be determined, even with relatively imprecise measuring methods, such as microelectrode mapping procedures.

As a result of concentrated efforts on a few favorable preparations, such as hand cortex in primates, we know a lot about the mutability of these structures. We also have enough evidence to say that many regions of cortex across many species of mammals are changeable, but we are uncertain if primary sensory cortex is more or less changeable than higher-order areas. However, there is evidence that cortical representations can be more mutable than subcortical representations.

The focus of this chapter is the effects of deactivating injuries to sensory systems, especially to the somatosensory system of primates. One reason for this focus is that the alterations in sensory inputs produced by damage have produced the largest changes in cortical organization, and thus the clearest evidence for plasticity in the mature brain has come from such deprivation experiments. Nevertheless, sensory experience and learning produce alterations in cortical circuits, and the accumulated evidence is now rather compelling (see chapter 16). However, we feel that the larger and more obvious changes produced by some types of injuries are especially interesting because they are not easily explained by simple adjustments in synaptic strengths. Thus the larger map reorganizations raise the issue of new neuronal growth in the mature brain. In addition, they raise the possibility of unwanted as well as desirable perceptual consequences.

Normally, sensory representations are relatively stable across time and across individuals

The hallmark of primary sensory cortex is the presence of an orderly and detailed representation of a sensory surface. It is the consistency of this representation across time and individuals that allows compelling evidence for mutability to be obtained. Thus the permanence of map organization allows changes that are due to a manipulation to be demonstrated by means of before-and-after measurements in the same animal, and it is the consistency of map organization across members of the same species that allows a group of normals to serve as controls for a group of manipulated individuals. While the variability of even primary sensory maps has been stressed on occasion (e.g., Merzenich et al., 1987), published maps of sensory cortex reflect measurement errors as well as biological variability. Cortical maps tend to be highly consistent in instances where measurement error is greatly reduced. Extreme consistency, for example, is apparent in the morphological reflection of the somatotopy of S1 in rats and mice, where the arrangement of the so-called barrel field is remarkably stable across individuals, at least those born with a normal number of facial whiskers (Welker and Van der Loos, 1986). A similar consistency across individuals has been reported for the anatomical isomorph in S1 of the nose of the star-nosed mole (Catania and Kaas, 1997). While some might argue that S1 in primates is more variable, we recently discovered that the representations of the fingers and palm are visible in appropriately processed brain sections through area 3b of monkeys, and this easily and accurately measured histological map is extremely consistent across individuals (Jain, Catania, and Kaas, 1998). Furthermore, the morphological map is not altered by manipulations that greatly change the physiological map, and thus the morphological map can serve as a reference for changes induced by manipulations. Even with the possibility of considerable measurement error, studies across laboratories, experimental groups, and recording conditions have revealed little variability in the response properties of neurons, the receptive field sizes of neurons, and the basic somatotopy revealed by neuronal populations in area 3b of macaque monkeys (Pons et al., 1987).

The dynamic nature of sensory maps

Any alteration in the pattern of input from a sensory surface would, of course, be immediately reflected in changes in the central maps activated by those inputs. But the changes are more complex than simple removals or additions because of convergences and divergences in the connection patterns and subtle differences in these patterns for excitatory and inhibitory connections. Thus removing the inputs from a finger with local anesthetic, for example, might not silence cortex or subcortical structures normally devoted to that finger because weak inputs to that cortex related to adjoining fingers might be less inhibited (Rasmussan and Turnbull, 1983; Kelahan and Doetsch, 1984; Calford and Tweedale, 1991; Pettit and Schwark, 1993; Rasmussan, Louw, and Northgrave, 1993; Doetsch et al., 1996). These immediate consequences of rebalancing inhibitory and excitatory circuits (see Xing and Gerstein, 1996; Nicolelis, 1997, for review) have been described as the "unmasking" of silent synapses (P. D. Wall, 1977) or more recently as "disinhibition" (Calford and Tweedale, 1988). The evidence for such immediate changes tells us a great deal about the nature of the circuits in the system and how they normally operate. Similar immediate changes in neuron receptive field properties, including receptive field sizes, can be induced by modifications in the activating stimuli. For example, the responses of visual neurons in visual cortex to line segments within the receptive field may be enhanced by similarly oriented line segments outside the receptive field, but inhibited by such segments of other orientations, suggesting a neural mechanism for the perceptual linking of line segments and the salience of segments of similar orientations. Many features of perception may depend on such dynamic features of cortical circuits (see Gilbert, 1998).

Other features of neurons and sensory maps may change rapidly with stimulus conditions. Many rapid changes may result from the modulation of local circuits by inputs from other structures (Castro-Alamancos and Connors, 1996). Brainstem neuromodulatory centers, such as the raphe nuclei and locus coeruleus, project widely to affect many neurons simultaneously as a result of changes in alertness, motivation, and emotional state (e.g., Juliano et al., 1990). In a similar but more focused manner, the activation of pain afferents by capsaicin injections in the skin appears to produce tonic activity in fibers that influence inhibitory interneurons and thus modulate receptive field sizes of neurons throughout the dorsal column–medial lemniscal system (Calford and Tweedale, 1991; Rasmusson, Louw, and Northgrave, 1993). Finally, synaptic strengths and thus neuronal properties and cortical maps can be rapidly modified by learning and experience (chapter 16; Weinberger, 1995; Ebner et al., 1997). Such stimulus-induced changes in synaptic strengths seem to depend on the entry of calcium into neurons through NMDA receptors following extended Hebbian rules (Bear, Cooper, and Ebner, 1987; Rauschecker, 1991; Benuskova, Diamond, and Ebner, 1994). During experience-related changes in mature brains, the synaptic modifications may be permitted or potentiated by the neuromodulatory actions of acetylcholine release via projections from nucleus basalis (Dykes, 1990, 1997; Juliano, Ma, and Eslin, 1991; Wienberger, 1995; Kilgard and Merzenich, 1998).

Slowly emerging reorganizations of cortical maps

Many alterations in sensory maps occur over longer time periods of hours, weeks, and even months. These more slowly emerging changes are especially interesting because they potentially involve mechanisms in addition to adjustments in the dynamic balance of the neuronal network and rapid synaptic modifications, especially activity-dependent effects on the expression of genes that can lead to neurotransmitter regulation (E. G. Jones, 1993) and the release of trophic factors (Levine and Black, 1997) that alter the growth of dendrites and axons. The products of early gene expression, as a result of increases or decreases in neural activity, can be measured in minutes to hours (e.g., Melzer and Steiner, 1997).

One of the now classic demonstrations of cortical plasticity involved the reorganization of the hand representation in S1 (3b) of monkeys after section of the median nerve to the skin of the thumb half of the glabrous hand (Merzenich et al., 1983a). This procedure deprives about half of the hand representation of its normal source of activation. Although some neurons in this deprived territory acquire new receptive fields on innervated parts of the hand immediately or very rapidly (Silva et al., 1996), probably due to disinhibition, the extent of the reactivation gradually increases over a period of weeks until all deprived neurons are highly responsive to tactile inputs on the hand (figure 15.1; Merzenich et al., 1983b). The recovery is largely from inputs from the hairy back of the hand, and the cortical reactivation is highly somatotopic, with regions formerly devoted to the glabrous surfaces of digits 1–3 activated instead from inputs from the dorsal skin of digits 1–3 in the same sequence.

The original interpretation of this recovery was that it was based on the potentiation of weak and ineffective synapses in the fringes of highly overlapping thalamocortical axon arbors, but subsequent studies have revealed that this interpretation is too simple. First, an investigation of the nature of the map of the hand in the first relay of tactile information in the cuneate nucleus of the dorsal column–trigeminal complex suggested an involvement at this initial level. Anatomical studies showed that afferents from each digit terminate in a separate cluster of neurons in the cuneate nucleus, but inputs from the dorsal and glabrous surfaces of the same digit terminate in the same cluster of cells (Florence, Wall, and Kaas, 1991). Thus it would require only a limited rewiring or potentiation of local connections in the cuneate nucleus for neurons responsive to glabrous skin to become responsive to dorsal skin. Second, reactivation of hand cortex can be incomplete if the radial nerve to the dorsal hand is sectioned in addition to the ulnar or median nerve to the glabrous hand (Garraghty et al., 1994), but reactivation is complete if both the ulnar and median nerves are sectioned (Garraghty and Kaas, 1991a). Thus the inputs from the dorsal hand are especially potent in reactivating cortex. Third, recordings obtained in the thalamic target of the cuneate nucleus, the hand subnucleus of the ventroposterior nucleus, revealed that considerable reactivation of deprived neurons occurs at this level of the system after median nerve section (Garraghty and Kaas, 1991b). More directly, reactivation of some of the deprived

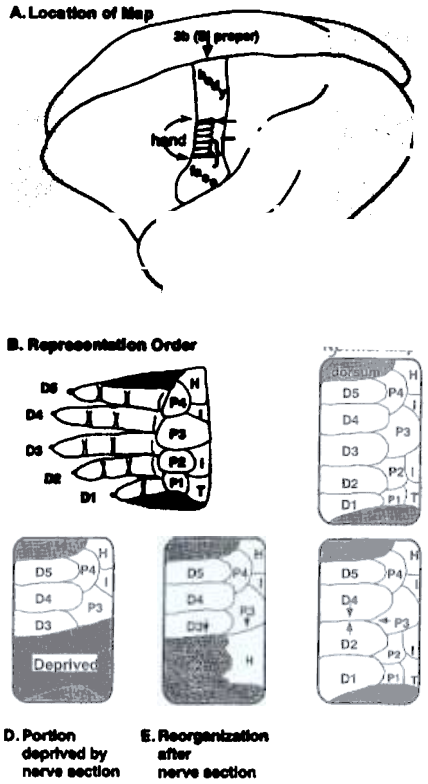

FIGURE 15.1 Primary somatosensory cortex (area 3b) reorganizes after median nerve section or finger loss in monkeys. (A) The locations of area 3b and the portion devoted to the hand on a lateral view of the brain of an owl monkey. This New World monkey has only a shallow dimple in cortex medial to the hand representation, rather than a central fissure, as in humans. Thus area 3b is largely in the exposed surface of the brain. (B) The glabrous hand is represented in area 3b as if the palm were split from the ventral wrist toward digit 3, and spread out on cortex with digits 1–5 in a lateromedial sequence and the palm caudal to the digits. The dorsal surface is poorly represented (stippled) in a variable manner. Often, the dorsal skin of the digits and hand are represented in narrow bands of tissue medial and lateral to that of the glabrous hand (see Jain, Florence, and Kaas, 1998, for review). (C) The hand representation is distorted into a roughly rectangular shape in area 3b, with a compression of the length compared to the width of the hand. (D) The median nerve subserves about half of the glabrous hand from the thumb (D1) to part of the middle finger (D3). Thus section of the median nerve deprives most of the lateral half of the hand representation of its normal source of activation (hatched region). (E) The deprived region of the hand representation, the former territory of the median nerve, becomes reactivated over about one month of recovery by inputs largely from the hairy, dorsal surface of the hand via the intact radial nerve. Some expansion of the representations of glabrous D3 and P3 occurs (arrows). The reactivation is somatotopic, with the former territories of glabrous D1–D3 and adjoining pads acquiring responsiveness to stimulation of dorsal skin of D1–D3 and adjoining pads (see Merzenich et al., 1983a, 1983b). (E) In another type of deprivation, the loss or removal of a finger, the deprived territory of the missing finger becomes responsive to inputs from the adjoining fingers and palm (see Merzenich et al., 1984; Jain, Catania, and Kaas, 1998). Digits and pads of the hand are traditionally numbered, and insular (I), hypothenar (H), and thenar (T) pads are indicated.

neurons occurs in the cuneate nucleus (Xu and Wall, 1997), as postulated. Yet, the outcome in cortex is not as simple as switching neurons in the cuneate nucleus from a glabrous to a hairy skin source of activation, together with the relay of this switch in activation to the thalamus and cortex. Instead, it seems likely that an incomplete and relatively weak reactivation of neurons in the cuneate nucleus is relayed and potentiated in the thalamus and potentiated again when relayed to the cortex. Much of this potentiation may depend on NMDA receptors, since chronically blocking these receptors prevented the reactivation and reorganization of somatosensory cortex (Garraghty and Muja, 1996). The reactivation of cortex may also be facilitated by the down-regulation of GABA expression in the deprived cortex as a consequence of a period of reduced neuronal activity (Garraghty, Lachica, and Kaas, 1991).

Whatever the mechanisms, the consequences of nerve damage can be completely reversible. If the median nerve is crushed, rather than sectioned, so that it can regenerate accurately to original skin targets, the regenerated nerve reclaims its lost cortical territory, and neurons in this territory recover receptive fields that are almost identical in skin locations to those they had originally (J. T. Wall, Felleman, and Kaas, 1983).

The series of experiments on the effects of median nerve damage in monkeys leads to several conclusions. First, subcortical structures are clearly subject to reorganization and reactivation. There is a history of earlier evidence for spinal cord and brainstem plasticity in adult mammals, but difficulties of measuring limited changes in the small subcortical maps led to uncertainties about at least some of the claims (see Snow and Wilson, 1991). The reactivation of the large hand subnucleus of the ventroposterior nucleus by preserved inputs from the back of the hand after median and ulnar nerve section provides strong evidence for subcortical plasticity (Garraghty and Kaas, 1991b), especially in conjunction with comparable results from a number of more recent studies (e.g., Pettit and Schwark, 1993; Rasmusson, 1996; Xu and Wall, 1997; Parker, Wood, and Dostrovsky, 1998). Second, normal map structure may differ from level to level in a processing system, so that relatively minor somatotopic adjustments at one level, such as the substitution of dorsal skin for glabrous skin inputs in the cuneate nucleus, can appear larger at subsequent levels (see Kaas and Florence, 1997). Third, modifications at early stages of processing in a hierarchical system can be amplified by modifications at subsequent stages. Even at early stages of cortical processing, the observed results involve a combination of cortical and subcortical mechanisms. Furthermore, due to feedback connections, cortical changes impact on subcortical representations (Ergenzinger et al., 1998). Nevertheless, we do not suggest that subcortical changes always play a major or even a notable role. We know, for example, that the second somatosensory area of monkeys, S2, depends on inputs from areas of anterior parietal cortex (Pons et al., 1987; Garraghty, Pons, and Kaas, 1990) and that lesions of the hand representations in these areas deactivate the hand portion of S2, which subsequently becomes responsive to other remaining inputs from anterior parietal cortex (Pons, Garraghty, and Mishkin, 1988; figure 15.2). It seems unlikely that the reorganization of S2 depends on subcortical rather than cortical mechanisms. We also know that restricted lesions of the retina in cats or monkeys deactivate the retinotopic portion of the thalamic relay, the lateral geniculate nucleus, and primary visual cortex, but the amount of reactivation by parts of the retina surrounding the lesion is very limited in the lateral geniculate nucleus (e.g., Darian-Smith and Gilbert, 1995; Baekelandt et al., 1994) compared to the extensive reactivation of cortex (figure 15.3; see Chino, 1997).

The subcortical and cortical changes in map organization demonstrated after peripheral nerve section in monkeys constitute only a fragment of an impressive collection of evidence that deactivations of populations of central nervous system neurons by receptor damage are followed by reactivations by remaining inputs. Positive results have been obtained from a range of manipulations across a number of mammalian species. In monkeys with amputated or missing digits, the primary somatosensory cortex normally responsive to those digits typically became responsive to inputs from adjoining digits (figure 15.1F), although some unresponsive cortex may remain (Merzenich et al., 1984; Calford and Tweedale, 1991; Code, Ealin, and Juliano, 1992; Manger, Woods, and Jones, 1996; Jain, Catania, and Kaas, 1998). Similarly, the cortical territories of

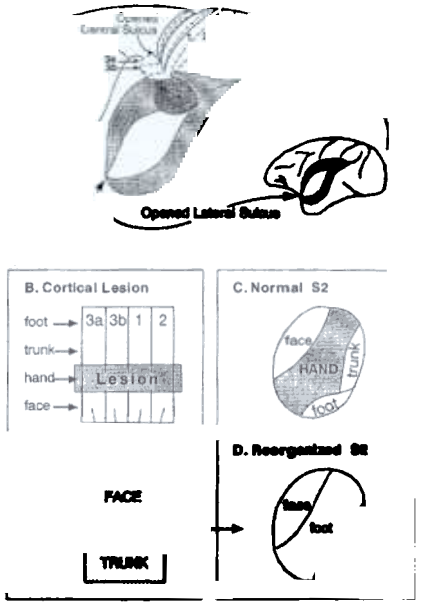

FIGURE 15.2 Reorganization of the second somatosensory area, S2, after lesions of the hand representations in anterior parietal cortex. Each of the four fields of anterior parietal cortex represents the body from foot to face in a mediolateral sequence (see Kaas, 1983). The activation of S2 depends on direct projections from these four fields, especially area 3b (Pons et al., 1987; Garraghty, Pons, and Kaas, 1990). Thus a lesion of the hand regions of these four fields deactivates the hand portion of S2. This cortex recovers responsiveness, largely to the foot (Pons, Garraghty, and Mishkin, 1988). (A) The locations of somatosensory areas on a lateral view of the brain of a macaque monkey. S2 can be seen on the upper bank of the opened lateral sulcus. Areas 3a and 3b are in the opened central sulcus, while areas 1 and 2 are largely on the brain surface. (B) A schematic of the four areas and S2, with the depriving effects of a lesion of hand cortex. (C) The normal somatotopy of S2 including a large representation of the hand. (D) The reorganized S2 with hand cortex reactivated by inputs from the foot.

missing digits of the large hand representations in S1 of raccoons became responsive to inputs from remaining digits (figure 15.4). Comparable results have been reported after digit loss in bats (Calford and Tweedale, 1988) and cats (Kalaska and Pomeranz, 1979) and after

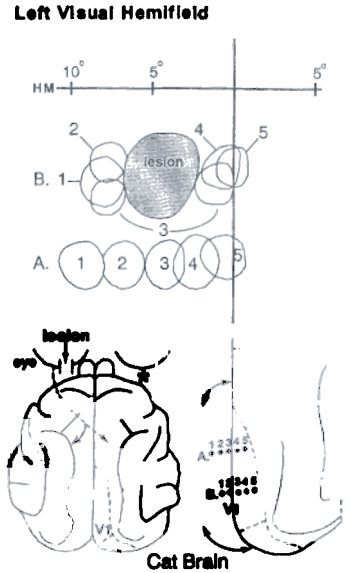

FIGURE 15.3 The reorganization of primary visual cortex following lesions of the retina. The deactivated cortex becomes responsive to parts of the retina adjoining the lesion. Because visual cortex is activated by both eyes, either lesions are retinotopically matched in both eyes, or all inputs are removed from the eye without a lesion (*) in order to completely deactivate a region of cortex.

(Lower left) A dorsal view of a cat brain showing a left eye with a 5° retinal lesion and the course of retinal projections (arrows) to the thalamus of both hemispheres. Recordings were made in primary visual cortex (V1–dashed line) of the right hemisphere.

(Lower right) A dorsal view of caudal visual cortex of the left hemisphere with some of V1 of the medial wall folded out, so that two rows of recording sites (numbered dots) are visible.

(Above) A portion of the left visual hemifield, marked in degrees along the zero horizontal meridian (HM), and showing the zero vertical meridian (VM). The projected location of the lesion of the retina of the left eye is outlined, together with receptive fields for neurons in the two rows of recording sites. Receptive fields for row A (see lower right) form a normal and orderly progression from temporal vision to the VM for a mediolateral sequence of recording sites toward the lateral border of V1. Receptive fields for row B, which passes through deprived cortex, are abnormally arranged so that receptive fields pile up on each side of the scotoma caused by the retinal lesion. Neurons at sites 2–4 acquired new receptive fields from retina outside of the lesion. Neurons at site 3 had two receptive fields, one on each side of the lesion. (Based on Kaas et al., 1990.)

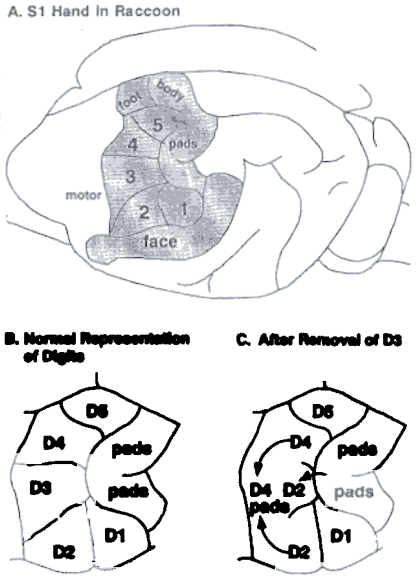

FIGURE 15.4 Reorganization of somatosensory cortex after digit removal has also been convincingly demonstrated in raccoons, which have a large, highly orderly representation of the glabrous hand in primary somatosensory cortex, S1. (A) The location of S1 and the hand representation of pads and digits 1–5 on a dorsolateral view of the brain. (B) Normal representation of the digits in S1. (C) After removal of D3, the deprived cortex becomes activated by inputs from D2 and D4, and the palm adjoining D3. (Based on Kelahan and Doetsch, 1984; Rasmusson, 1982).

nerve damage in rats (J. T. Wall and Cusick, 1984). Cortical reorganization has been demonstrated even in humans, but the limited resolution of the noninvasive brain-imaging techniques (fMRI) has meant that only the larger reorganizations following limb amputations are obvious (see next section). While studies of cortex have concentrated on the detailed somatotopic map in S1 (3b), reorganizations have also been demonstrated in areas 3a and 1 of anterior parietal cortex (Merzenich et al., 1983a; Jain, Catania, and Kaas, 1997a) and in S2 (figure 15.2; Pons, Garraghty, and Mishkin, 1988) of monkeys.

As already noted, there have been many demonstrations of the filling in of cortical zones of deactivation after focal lesions of the retina in cats and monkeys (figure 15.3; Chino, 1997), and there is some evidence for the reorganization of the middle temporal visual area, MT, of monkeys after partial lesions of MT (Newsome and Pare, 1988; Yamasaki and Wurtz, 1991) or lesions of its activating input from V1 (Kaas and Krubitzer, 1992). An advantage of the visual system for studies of reactivation is that the reactivated neurons can be easily studied quantitatively for changes in response properties. Consistent with the qualitative observations from somatosensory cortex, visual neurons that acquire new receptive fields as a result of retinal lesions are little changed in response properties (Chino et al., 1995; Chino, 1997). Primary auditory cortex has also been shown to reorganize (see Kaas, 1996) after partial hearing loss in adult rodents (Robertson and Irvine, 1989), cats (Rajan et al., 1993), and monkeys (figure 15.5; Schwaber, Garraghty, and Kaas, 1993).

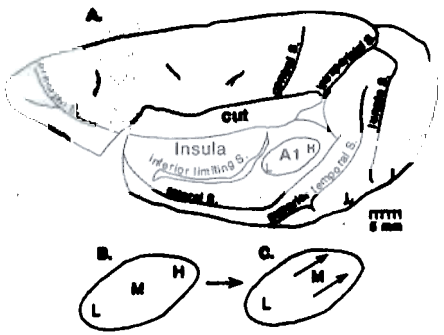

FIGURE 15.5 The reorganization of deactivated auditory cortex. (A) A dorsal view of the left hemisphere of a macaque monkey brain with cortex over the lower bank of the lateral sulcus (S) cut away to reveal the location of primary auditory cortex (A1). (B) Primary auditory cortex (oval) normally is tonotopically organized in roughly rostrocaudal fashion with low tones (L) activating rostral locations, middle frequency tones (M) activating middle locations, and high tones (H) activating caudal locations. (C) Months after a high-frequency cochlear hearing loss produced by ototoxic drugs, neurons in caudal A1 no longer responded to high tones. Instead, these neurons responded to middle-frequency tones, and the representation of middle tones expanded (arrows). (Based on Schwaber, Garraghty, and Kaas, 1993).

Evidence for plasticity in primary motor cortex comes from microstimulation experiments where a systematic map of movements can be demonstrated by evoking movements from many locations in cortex with low levels of electrical stimulation delivered with microelectrodes. After the loss of the muscle targets of part of motor cortex (Donoghue, Suner, and Sanes, 1990; Sanes, Suner, and Donoghue, 1990) by section of the motor nerve to the movable whiskers of the face in rats, low levels of electrical stimulation of the vibrissa cortex come to evoke movements of the forelimb and eye (figure 15.6). Similar reorganizations of human motor cortex have been demonstrated with transcranial magnetic stimulation (see Chen et al., 1998), and in monkeys with microstimulation (Schieber and Deuel, 1997). Additionally, lesions of parts of M1 for specific movements are followed by recoveries where stimulation of remaining parts of M1 can evoke the movements of the missing cortex (Nudo and Milliken, 1996; Nudo et al., 1996; Nudo, Plautz, and Milliken, 1997). Thus we conclude from these rather dramatic experiments that the mature brain, perhaps especially cortex, is not fixed in functional organization, and cortical areas of several levels in all major systems and across mammalian species can change.

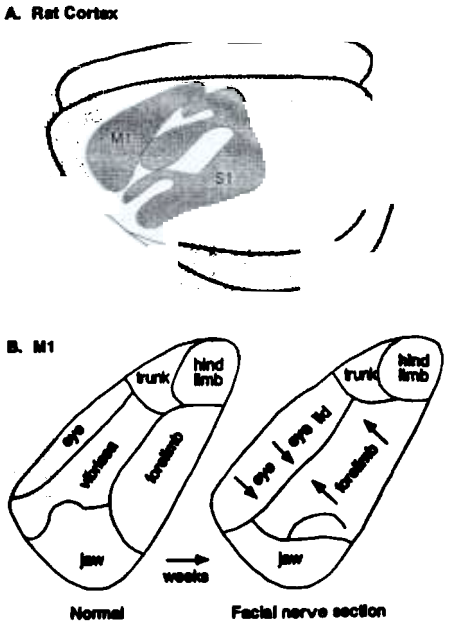

FIGURE 15.6 The reorganization of primary motor cortex, M1, after section of the motor nerve to the movable vibrissa of the face. (A) A dorsolateral view of a rat brain showing the locations of primary motor cortex, M1, and somatosensory cortex, S1. (B) The normal somatotopy of the motor map in M1 (left) is modified over weeks of recovery after nerve section so that electrical stimulation of vibrissa cortex comes to evoke movements of the forelimb, eyelid, and eye. (Based on Sanes, Suner, and Donoghue, 1990).

Massive cortical reorganization

Most of the changes in sensory and motor representations described are of a size that is limited enough to be compatible with explanations based largely or solely on alterations in the synaptic strengths of existing connections. Recently, however, there have been a number of demonstrations of cortical reorganizations of a very large scale following the loss of most or all of the afferent inputs from a limb or even larger portions of the body. The first evidence that such massive changes occur come from studies of somatosensory cortex in monkeys 12 years or more after complete deafferentation of the arm by section of the relevant dorsal roots as they enter the spinal cord. Originally, these monkeys were studied behaviorally. Fortunately some were available for a microelectrode mapping study of somatosensory cortex. The surprising and remarkable finding from these recordings was that the large mediolateral extents (10 mm or more) of areas 3b and 1 that formerly represented the hand, wrist, and arm in these monkeys, were completely responsive to inputs from the chin and jaw (Pons et al., 1991). Thus neurons over a large expanse of cortex responded vigorously to the displacement of hairs and light touch on a limited portion of the face. The reactivated cortex was just medial to cortex that normally responds to the face, and this cortex continued to respond to the face. These results raised two important questions. First, what are the perceptual consequences of such an extensive reorganization of the somatosensory system? Second, how is such an extensive reorganization mediated?

The evidence for massive cortical reorganization immediately attracted the attention of investigators interested in the sensation of the existence of a missing limb, the phantom limb, that is typically reported by adult humans with amputations. The existence of such sensations has long been recognized, and they have been attributed to spontaneous or other neural activity in the portions of the somatosensory system formerly related to the missing limb (e.g., Melzack, 1990). Soon after the report on cortical reorganization in monkeys, Ramachandran, Rogers-Ramachandran, and Stewart (1992) drew attention to highly significant behavioral observations on phantom limbs. In brief, they noted that a light touch on the face of a patient with a missing arm led to the sensation of touch, not only on the face, but also on the phantom of the missing arm. Furthermore, touches on different parts of the face resulted in sensations on different parts of the phantom. To explain these observations, Ramachandran, Rogers-Ramachandran, and Stewart (1992) assumed that amputations are followed by massive cortical reorganization, as in deafferented monkeys. They further postulated that touching the face activates the reorganized cortex, and activation of the reorganized cortex signals touch on the missing limb, rather than the real source of activation, the face. Further study revealed that sensations on the missing limb can also be triggered by touches on the skin of the stump of the missing limb (Ramachandran, 1993; Halligan et al., 1993; Yang et al., 1994; Aglioti, Bonazzi, and Cortese, 1994). However, the hypothesis that the triggered phantom sensations are caused by the activation of reorganized parts of primary somatosensory cortex does not easily account for all observations on phantom limbs. Most notably, trigger zones on the arm can emerge for sensations referred to a missing hand within a day of the loss of the hand (Doetsch, 1997). As yet, there is no evidence for such rapid reactivation of primary somatosensory cortex (see below).

At the time when Ramachandran, Rogers-Ramachandran, and Stewart (1992) proposed that the face activated hand cortex in humans with forelimb amputation, such extensive reorganization of cortex was only known for monkeys with a complete deafferentation of the forelimb (Pons et al., 1991), and it was not certain what would happen after a more limited sensory loss. However, monkeys, like humans, sometimes receive injuries that require a therapeutic amputation of a limb, and it soon became possible to study cortical organization in three such monkeys. Microelectrode recordings from these monkeys with forelimb or hand amputations revealed that hand cortex was completely reactivated by inputs from the stump of the limb, and to some extent the face (Florence and Kaas, 1995). The results indicated that massive reorganization of somatosensory cortex can follow the loss of inputs from the hand or forelimb in primates (also see Florence, Taub, and Lyon, 1997), and thus cortical reorganization could account for the face and stump trigger zones for sensations on the phantom in humans. Unfortunately, the results did not provide any information on the length of time it takes for reorganization, since the monkeys were studied 1–13 years after their amputations. However, the results did provide an important clue about the possible sources of the reactivation. In each monkey, an anatomical tracer was injected into the skin of the stump of the amputated limb. The transportation of this tracer through sensory nerves of the stump to the spinal cord and cuneate subnucleus of the brain stem revealed axon terminations in normal locations for the representation of the arm, but also a sparse distribution of axons in the part of the nucleus where the hand is normally represented. These anatomical results generated the hypothesis that axons from the arm had sprouted to grow into the deafferented part of the cuneate nucleus formerly devoted to the hand. While this sparse reinnervation presumably would activate only some of the deprived neurons on the cuneate nucleus, the divergence and convergence of projections from the cuneate nucleus to the ventroposterior nucleus of the thalamus would result in a larger population of reactivated neurons, and the divergence of thalamocortical projections, together with the framework of lateral, intrinsic connections in somatosensory cortex, would lead to more effective reactivations at these higher levels.

The use of noninvasive imaging methods has allowed the issue of brain reorganization after amputations to be directly examined in humans. Such imaging studies provided further evidence that face and stump inputs come to activate hand cortex in humans with forelimb amputations (Yang et al., 1994; Elbert et al., 1994; Flor et al., 1995; Knecht et al., 1996). Remarkable additional evidence came from a study of the results of recording from neurons in the ventroposterior nucleus of humans with amputations, and electrically stimulating the same neurons (Davis et al., 1998). In normal, undeprived portions of the somatosensory thalamus, these investigators found that the sensations produced by microstimulation were referred to the same locations as the receptive fields of the neurons at the sites of electrical stimulation. But in some amputees, stimulating neurons with receptive fields on the stump of the missing limb produced sensations referred to the missing limb. The results indicate that reorganization of deprived parts of the somatosensory system, as observed in cortex, had already occurred at the level of the thalamus, and that the reactivated neurons continued to retain their original meaning of stimuli on the missing limb. This finding, of course, does not suggest that sensations on the missing limb are mediated in the thalamus, since these neurons are part of a complex system that includes many levels of somatosensory cortex that would also be activated by the electrical stimulation of thalamic neurons. Nevertheless, the evidence is now rather compelling that amputations can produce extensive reorganizations of the somatosensory system. Such reorganizations may be expressed subcortically at the level of the thalamus, and reactivated neurons retain the original significance and signal misperceptions of touch on the phantom limb.

Are such massive reactivations mediated, at least to some critical extent, by the growth of new connections? Further evidence for new growth came from studies of the time it takes for massive cortical reorganization, since new growth would take some time to occur. The time course of reactivation was possible to study in monkeys with unilateral section of forelimb afferents in the dorsal columns of the spinal cord (Jain, Catania, and Kaas, 1997b, 1998a). There is a history of many years of behavioral and electrophysiological studies of the effects of dorsal column section in monkeys, and a surprising finding is that the behavioral consequences are rather mild (e.g., Makous, Friedman, and Vierch, 1996). Thus, soon after unilateral sections, monkeys climb about and retrieve food with the affected limb, although not as skillfully as with the normal limb. Despite these rather limited behavioral changes, the hand region of area 3b of somatosensory cortex of monkeys was completely deactivated by dorsal column section above the level where afferents enter from the hand, while the more lateral cortex devoted to the face responded normally to touch on the face (figure 15.7B). However, if the lesion was incomplete so that a fraction of the afferents from the hand remained, these afferents continued to activate cortical neurons, and the complete hand territory of cortex gradually became reactivated by these preserved inputs from the hand (figure 15.7D, E). If the dorsal column section was complete, no reactivation of this cortex by hand afferents occurred even after months. Instead, the hand cortex became reactivated by preserved inputs from the face and a few preserved afferents from the anterior arm that enter the spinal cord above the level where afferents enter from the hand (figure 15.7C). Indeed, many neurons in hand cortex became responsive to tactile stimuli on either the face or anterior arm. Most importantly, the reactivation of somatosensory cortex by face inputs occurred slowly, emerging only after six to eight months of recovery. This slow development suggests that a critical feature in the reactivation is the sprouting and growth of new connections, possibly the sprouting and growth of axon collaterals of afferents from the face (and stump for amputations) into the portions of the cuneate nucleus of the brain stem normally activated by the hand as proposed by Florence and Kaas (1995).

The proposal that reactivation is based on the formation of new connections is somewhat unconventional, since new growth in the mature central nervous system is expected to be very limited (see Florence and Kaas, in press, for review). Yet, there is evidence that the terminations of crushed nerves sprout in the spinal cord of monkeys (Florence et al., 1993; see Kapfhammer, 1997, for review of axon sprouting in the spinal cord) and that afferents grow into new brainstem territories after limb amputations (Florence and Kaas, 1995) or dorsal column section (N. Jain, unpublished observations). Since the new growth in the brain stem is sparse, the effects of these reinnervations are most likely enhanced at higher levels in the system so that many neurons are

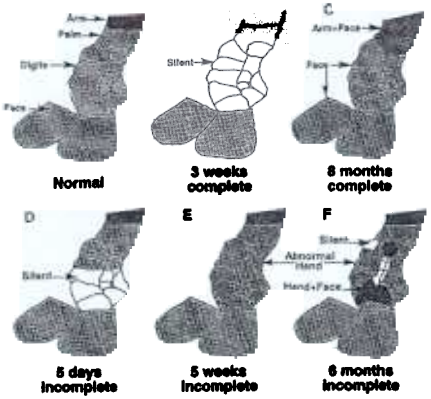

FIGURE 15.7 The reorganization of somatosensory cortex after dorsal column lesions. The dorsal column constitutes the major spinal cord pathway for ascending afferents from cutaneous and muscle receptors. Section of the dorsal column at high cervical levels removes this input from the hand and most of the arm, as well as lower parts of the body, while leaving inputs from the face intact. (A) The normal organization of the lateral portion of area 3b in owl monkeys (see figure 15.1 for locations on brain). The upper and lower face are represented in two ovals of cortex laterally, the digits in a lateromedial sequence from 1–5 more medially and rostrally, the pads of the palm, caudally, and the wrist and arm medially. (B) After a complete dorsal column lesion of one side, the opposite hand region and more medial cortex becomes completely unresponsive to touch and hair movement. Some medial cortex may remain responsive to preserved inputs from the anterior arm, and lateral cortex remains normally responsive to touch and hair movement on the face. This complete deactivation persists for months. (C) After 6–8 months of recovery from contralateral dorsal column section, hand cortex becomes responsive to touch and hair movement on the face. Some of the more medial cortex may respond to both the face and the anterior arm. (D) Incomplete dorsal column lesions leave some of the hand representation responsive to tactile stimulation of the hand. Within the first few days of recovery, this activation is somatotopically appropriate, and much of the hand representation is unresponsive (Silent). (E) Within weeks of an incomplete dorsal column lesion leaving some inputs from the hand intact, these preserved inputs come to activate much or all of hand cortex. (F) After months of recovery after an incomplete dorsal column lesion, many locations in hand cortex respond to both hand and face inputs. This result seems to reflect both the more rapid potentiation of preserved inputs from the hand and the slower potentiation of preserved inputs from the face. (Modified from Jain, Florence, and Kaas, 1998.)

reactivated in the thalamus (Davis et al., 1998), and the cortical reactivation is even more effective. Reactivations in cortex may even depend in part on the growth of new connections in cortex. Darian-Smith and Gilbert (1994) provided anatomical evidence that the horizontal connections in visual cortex sprout to become more dense in regions where neurons have become reactivated after being deprived by long-standing retinal lesions. Similarly, injections of anatomical tracers in somatosensory cortex of monkeys with limb amputations provided evidence for the growth of new and more extensive horizontal connections within the deprived but recovered cortex (Florence, Taub, and Lyon, 1997). New growth may occur at other levels of the somatosensory and visual systems as well (e.g., Baekelandt et al., 1994), and new growth may include the extension of dendrites of cortical and subcortical neurons (e.g., T. A. Jones and Schallert, 1994).

The anatomical results after massive deafferentations demonstrate the possibility of considerable new growth in the mature central nervous system (also, see Aguayo, 1985). Glial cells of the central nervous system appear to generate molecules that normally inhibit axon growth, and thus new growth can be promoted by interfering with these molecules (e.g., Z'Graggen et al., 1998; see Schwab, 1996, for review). It is not certain why new growth of an extensive nature takes so long to emerge, but it may take time for inducing factors (e.g., Cohen-Cory and Fraser, 1995) to be expressed, as well as time for new growth (see Florence and Kaas, in press). While new growth may be important in many reactivations, new growth may provide only a framework for recovery, and many other factors important in less massive reactivations undoubtedly also contribute.

Conclusions

As a result of a large number of studies of cortical and subcortical plasticity of sensory and motor systems in adult mammals, especially during the last few years, a number of conclusions are now supportable.

1. The detailed structure of normal representations is dynamically maintained. Alterations in inputs, activations of modulating systems with emotional state and attention, and even changes in stimulus conditions can produce immediate changes in the dynamic balance within systems so that receptive field properties, receptive field sizes and locations, and map topography change. Such rapid changes are typically quite reversible, but they may lead to changes in synaptic strengths and thus to more persistent alterations.

2. Alterations produced by prolonged, localized sensory or electrical stimulation or by sensory deprivations may lead to activity-induced modifications in neurotransmitter and neuromodulator expression, the local growth of axons and dendrites, and alterations in synaptic strengths. Synaptic weights also may be altered by experience and learning according to modified Hebbian rules.

3. Reorganizations of sensory and motor maps occur in all major systems and at subcortical as well as cortical levels. Modifications accumulate and amplify across serial levels of processing. Cortical areas, due to a system of horizontal connections, may be more modifiable than subcortical stations.

4. Some types of recovery are best understood in terms of the internal structures of subcortical maps. The substitution of dorsal skin inputs for glabrous skin inputs, for example, appears to involve rather local and limited synaptic changes in the cuneate nucleus of the brain stem that results in an impressively large reorganization of the cortical map.

5. Some types of reorganization, such as those that occur after major sensory deafferentations, take months to emerge. These major reactivations appear to depend on the extensive sprouting and growth of axons to form new connections. The massive reorganizations lead to misperceptions, and often unwanted sensations. Nevertheless, the potential for new growth holds promise for many clinical applications, and new growth may be important in other recoveries, such as those that occur after stroke.

REFERENCES

AGLIOTI, S., A. BONAZZI, and F. CORTESE, 1994. Phantom lower limb as a perceptual marker of neural plasticity in the mature human brain. *Proc. R. Soc. Lond. B.* 255:273–278.

AGUAYO, A. J., 1985. Axonal regeneration from injured neurons in the adult mammalian central nervous system. In *Synaptic Plasticity*, C. W. Cotman, ed. New York: Guilford Press, pp. 457–484.

BAEKELANDT, V., L. ARCKEN, W. ANNAERT, U. T. EYSEL, G. A. ORBAN, and F. VANDESANDE, 1994. Alterations in GAP-43 and synapsin immunoreactivity provide evidence for synaptic reorganization in adult cat dorsal lateral geniculate nucleus following retinal lesions. *Eur. J. Neurosci.* 6:754–765.

BEAR, M. F., L. N. COOPER, and F. F. EBNER, 1987. A physiological basis for a theory of synapse modification. *Science* 237:42–48.

BENUSKOVA, L., M. E. DIAMOND, and F. F. EBNER, 1994. Dynamic synaptic modification threshold: Computational model of experience-dependent plasticity in adult rat barrel cortex. *Proc. Natl. Acad. Sci. U.S.A.* 91:4791–4795.

CALFORD, M. B., and R. TWEEDALE, 1988. Immediate and chronic changes in responses of somatosensory cortex in adult flying-fox after digit amputation. *Nature* 332:446–448.

CALFORD, M. B., and R. TWEEDALE, 1991. Immediate expansion of receptive fields of neurons in area 3b of macaque monkeys after digit denervation. *Somatosens. Mot. Res.* 8:249–260.

CASTRO-ALAMANCOS, M. A., and B. W. CONNORS, 1996. Short-term plasticity of a thalamocortical pathway dynamically modulated by behavioral state. *Science* 272:274–277.

CATANIA, K. C., and J. H. KAAS, 1997. Somatosensory fovea in the star-nosed mole: Behavioral use of the star in relation to innervation patterns and cortical representation. *J. Comp. Neurol.* 387:215–233.

CHEN, R., B. CORNWELL, Z. VASEEN, M. HALLETT, and L. G. COHEN, 1998. Mechanisms of cortical reorganization in lower-limb amputees. *J. Neurosci.* 18:3443–3450.

CHINO, Y. M., 1997. Receptive-field plasticity in the adult visual cortex: Dynamic signal recording or experience-dependent plasticity. *Sem. Neurosci.* 9: 34–46.

CHINO, Y. M., E. L. SMITH III, J. H. KAAS, Y. SASAKI, and H. CHENG, 1995. Receptive-field properties of deafferented visual cortical neurons after topographic map reorganization. *J. Neurosci.* 15:2417–2433.

CODE, R. A., D. E. ESLIN, and S. L. JULIANO, 1992. Expansion of stimulus-evoked metabolic activity in monkey somatosensory cortex after peripheral denervation. *Exp. Brain Res.* 88:341–344.

COHEN-CORY, S., and S. E. FRASER, 1995. Effects of brain-derived neurotrophic factor on optic axon branching and remodelling *in vivo*. *Nature* 378:192–196.

DARIAN-SMITH, C., and C. D. GILBERT, 1994. Axonal sprouting accompanies functional reorganization in adult cat striate cortex. *Nature* 368:737–740.

DARIAN-SMITH, C., and C. D. GILBERT, 1995. Topographic reorganization in the striate cortex of the adult cat and monkey is cortically mediated. *J. Neurosci.* 15:1631–1647.

DAVIS, K. D., Z. H. T. KISS, L. LUO, R. R. TASKAR, A. M. LOZANO, and J. O. DOSTROVSKY, 1998. Phantom sensations generated by thalamic microstimulation. *Nature* 391:385–387.

DOETSCH, G. S., 1997. Progressive changes in cutaneous trigger zones for sensation referred to a phantom hand: A case report and review with implications for cortical reorganization. *Somatosens. Mot. Res.* 14:6–16.

DOETSCH, G. S., T. A. HARRISON, A. C. MACDONALD, and M. S. LITAKER, 1996. Short-term plasticity in primary somatosensory cortex of the rat: Rapid changes in magnitudes and latencies of neuronal response following digit denervation. *Exp. Brain Res.* 112:505–512.

DONOGHUE, J. P., S. SUNER, and J. N. SANES, 1990. Dynamic organization of primary motor cortex output to target muscles in adult rats. II. Rapid reorganization following motor nerve lesions. *Exp. Brain Res.* 79:492–503.

DYKES, R. W., 1990. Acetylcholine and neuronal plasticity in somatosensory cortex. In *Brain Cholinergic Systems*, M. Steriade and D. Biesold, eds. New York: Oxford University Press, pp. 294–313.

DYKES, R. W., 1997. Mechanisms controlling neuronal plasticity in somatosensory cortex. *Can. J. Physiol. Pharmacol.* 75: 535–545.

EBNER, F. F., V. REMA, R. SACHDEV, and F. J. SYMONS, 1997. Activity-dependent plasticity in adult somatic sensory cortex. *Sem. Neurosci.* 9:47–58.

ELBERT, T., H. FLOR, N. BIRBAUMER, et al., 1994. Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury. *NeuroReport* 5:2593–2597.

ERGENZINGER, E. R., M. M. GLASIER, J. O. HAHM, and T. P. PONS, 1998. Cortically induced thalamic plasticity in the primate somatosensory system. *Nature Neurosci.* 1:226–229.

FLOR, H., T. ELBERT, and S. KNECHT, et al., 1995. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* 375:482–484.

FLORENCE, S. L., P. E. GARRAGHTY, M. CARLSON, and J. H. KAAS, 1993. Sprouting of peripheral nerve axons in the spinal cord of monkeys. *Brain Res.* 601:343–348.

FLORENCE, S. L., and J. H. KAAS, 1995. Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. *J. Neurosci.* 15:8083–8095.

FLORENCE, S. L., and J. H. KAAS, in press. Cortical plasticity: Growth of new connections can contribute to reorganization. In *Somatosensory Processing: From Single Neurons to Brain Imaging*. M. J. Rowe, ed. North Ryde, New South Wales: Gordon and Breach Science.

FLORENCE, S. L., H. B. TAUB, and D. C. LYON, 1997. Functional and structural reorganization in somatosensory cortex of adult macaque monkeys after forelimb injury. *Soc. Neurosci. Abstr.* 23:1007.

FLORENCE, S. L., J. T. WALL, and J. H. KAAS, 1991. Central projections from the skin of the hand in squirrel monkeys. *J. Comp. Neurol.* 311:563–578.

FOOTE, S. L., and J. H. MORRISON, 1987. Extrathalamic modulation of cortical function. *Annu. Rev. Neurosci.* 10:67–95.

GARRAGHTY, P. E., D. P. HANES, S. L. FLORENCE, and J. H. KAAS, 1994. Pattern of peripheral deafferentation predicts reorganizational limits in adult primate somatosensory cortex. *Somatosens. Mot. Res.* 11:109–117.

GARRAGHTY, P. E., and J. H. KAAS, 1991a. Large-scale functional reorganization in adult monkey cortex after peripheral nerve injury. *Proc. Natl. Acad. Sci. U.S.A.* 88:6976–6980.

GARRAGHTY, P. E., and J. H. KAAS, 1991b. Functional reorganization in adult monkey thalamus after peripheral nerve injury. *NeuroReport* 2:747–750.

GARRAGHTY, P. E., E. A. LACHICA, and J. H. KAAS, 1991. Injury-induced reorganization of somatosensory cortex is accompanied by reductions in GABA staining. *Somatosens. Mot. Res.* 8:347–354.

GARRAGHTY, P. E., and N. MUJA, 1996. NMDA receptors and plasticity in adult primate somatosensory cortex. *J. Comp. Neurol.* 367:319–326.

GARRAGHTY, P. E., T. P. PONS, and J. H. KAAS, 1990. Ablations of areas 3b (S1 proper) and 3a of somatosensory cortex in marmosets deactivate the second and parietal ventral somatosensory areas. *Somatosens. Mot. Res.* 7:125–135.

GILBERT, C. D., 1998. Adult cortical dynamics. *Physiol. Rev.* 78:467–485.

HALLIGAN, P. W., J. C. MARSHALL, D. T. WADE, J. DAVY, and D. MORRISON, 1993. Thumb in cheek? Sensory reorganizations and perceptual plasticity after limb amputation. *NeuroReport* 4:233–236.

JAIN, N., K. C. CATANIA, and J. H. KAAS, 1997a. Reorganization of somatosensory area 3a in owl monkeys following long-term deafferentation by dorsal column section. *Soc. Neurosci. Abstr.* 23:1799.

JAIN, N., K. C. CATANIA, and J. H. KAAS, 1997b. Deactivation and reactivation of somatosensory cortex after dorsal spinal cord injury. *Nature* 386:495–498.

JAIN, N., K. C. CATANIA, and J. H. KAAS, 1998. A histologically visible representation of the fingers and palm in primate area 3b and its immutability following long-term deafferentations. *Cerebral Cortex* 8:227–236.

JAIN, N., S. L. FLORENCE, and J. H. KAAS, 1998. Reorganization of somatosensory cortex after nerve and spinal cord injury. *News Physiol. Sci.* 13:143–149.

JONES, E. G., 1993. GABAergic neurons and their role in cortical plasticity in primates. *Cerebral Cortex* 3:361–372.

JONES, T. A., and T. SCHALLERT, 1994. Use-dependent growth of pyramidal neurons after neocortical damage. *J. Neurosci.* 14:2140–2152.

JULIANO, S. L., W. MA, M. F. BEAR, and D. ESLIN, 1990. Cholinergic manipulation alters stimulus-evoked metabolic activity in cat somatosensory cortex. *J. Comp. Neurol.* 297:106–120.

JULIANO, S. L., W. MA, and D. ESLIN, 1991. Cholinergic depletion prevents expansion of topographic maps in somatosensory cortex. *Proc. Natl. Acad. Sci. U.S.A.* 88:780–784.

KAAS, J. H., 1983. What, if anything, is S-I? The organization of the "first somatosensory area" of cortex. *Physiol. Rev.* 63:206–231.

KAAS, J. H., 1996. Plasticity of sensory representations in the auditory and other systems of adult mammals. In *Auditory System Plasticity and Regeneration*, R. J. Salvi, D. Henderson, F. Fiorino, and J. Colletti, eds. New York: Thieme Medical, pp. 213–223.

KAAS, J. H., and S. L. FLORENCE, 1997. Mechanisms of reorganization in sensory systems of primates after peripheral nerve injury. In *Brain Plasticity*, H. J. Freund, B. A. Sabel, and O. W. Witte, eds. *Advances in Neurology*, vol. 73. Philadelphia: Lippincott-Raven Press, pp. 147–158.

KAAS, J. H., and L. A. KRUBITZER, 1992. Area 17 lesions deactivate area MT in owl monkeys. *Vis. Neurosci.* 9:399–407.

KAAS, J. H., L. A. KRUBITZER, Y. M. CHINO, A. L. LANGSTON, E. H. POLLEY, and N. BLAIR, 1990. Reorganization of retinotopic cortical maps in adult mammals after lesions of the retina. *Science* 248:229–231.

KALASKA, J., and B. POMERANZ, 1979. Chronic paw denervation causes an age-dependent appearance of novel responses from forearm in "paw cortex" of kittens and adult cats. *J. Neurophysiol.* 42:618–633.

KAPFHAMMER, J. P., 1997. Axon sprouting in the spinal cord: Growth promoting and growth inhibitory mechanisms. *Anat. Embryol.* 196:417–426.

KELAHAN, A. M., and G. S. DOETSCH, 1984. Time-dependent changes in the functional organization of somatosensory cerebral cortex following digit amputation in adult raccoons. *Somatosens. Res.* 2:49–81.

KILGARD, M. P., and M. M. MERZENICH, 1998. Cortical map reorganization enabled by nucleus basalis activity. *Science* 279:1714–1718.

KNECHT, S. H., T. HENNINGSEN, H. ELBERT, H. FLOR, C. HOHLING, C. PANTEV, and E. TAUB, 1996. Reorganizational and perceptional changes after amputation. *Brain* 119:1213–1219.

LEVINE, E. S., and I. B. BLACK, 1997. Trophic factor, synaptic plasticity, and memory. *Ann. N.Y. Acad. Sci.* 835:12–19.

MAKOUS, J. C., R. M. FRIEDMAN, and C. J. VIERCK, 1996. Effects of a dorsal column lesion on temporal processing within the somatosensory system of primates. *Exp. Brain Res.* 112: 253–267.

MANGER, P. P., T. M. WOODS, and E. C. JONES, 1996. Plasticity of the somatosensory cortical map in macaque monkeys after chronic partial amputation of a digit. *Proc. R. Soc. Lond. B.* 263:933–939.

MELZACK, R., 1990. Phantom limbs and the concept of a neuromatrix. *Trends Neurosci.* 13:88–92.

MELZER, P., and H. STEINER, 1997. Stimulus-dependent expression of immediate-early genes in rat somatosensory cortex. *J. Comp. Neurol.* 380:145–153.

MERZENICH, M. M., J. H. KAAS, J. WALL, J. J. NELSON, M. SUR, and D. FELLEMAN, 1983a. Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation. *Neurosci.* 8:33–55.

MERZENICH, M. M., J. H. KAAS, J. T. WALL, M. SUR, R. J. NELSON, and D. J. FELLEMAN, 1983b. Progression of change following median nerve section in the cortical representation of the hand in areas 3b and 1 in adult owl and squirrel monkeys. *Neurosci.* 10:639–665.

MERZENICH, M. M., R. J. NELSON, J. H. KAAS, M. P. STRYKER, W. M. JENKINS, J. M. ZOOK, M. S. CYNADER, and A. SCHOPPMANN, 1987. Variability in hand surface representation in areas 3b and 1 in adult owl and squirrel monkeys. *J. Comp. Neurol.* 25:281–296.

MERZENICH, M. M., R. J. NELSON, M. P. STRYKER, M. S. CYNADER, A. SCHOPPMAN, and J. M. ZOOK, 1984. Somatosensory cortical map changes following digit amputation in adult monkeys. *J. Comp. Neurol.* 224:591–605.

NEWSOME, W. T., and E. B. PARE, 1988. A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *J. Neurosci.* 8:2201–2211.

NICOLELIS, M. A. L., 1997. Dynamic and distributed somatosensory representations as the substrate for cortical and subcortical plasticity. *Sem. Neurosci.* 9:24–33.

NUDO, R. J., and G. W. MILLIKEN, 1996. Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. *J. Neurophysiol.* 75:2144–2149.

NUDO, R. J., E. J. PLANTZ, and G. W. MILLIKEN, 1997. Adaptive plasticity in primate motor cortex as a consequence of behavioral experience and neuronal injury. *Sem. Neurosci.* 9:13–23.

NUDO, R. J., B. M. WISE, F. SIFUENTES, and G. W. MILLIKEN, 1996. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science* 272: 1791–1794.

PARKER, J. L., M. L. WOOD, and J. O. DOSTROVSKY, 1998. A focal zone of thalamic plasticity. *J. Neurosci.* 18:548–558.

PETTIT, M. J., and H. D. SCHWARK, 1993. Receptive field reorganization in dorsal column nuclei during temporary denervation. *Science* 262:2054–2056.

PONS, T. P., P. E. GARRAGHTY, D. P. FRIEDMAN, and M. MISHKIN, 1987. Physiological evidence for serial processing in somatosensory cortex. *Science* 237:417–420.

PONS, T. P., P. E. GARRAGHTY, and M. MISHKIN, 1988. Lesion-induced plasticity in the second somatosensory cortex of adult macaques. *Proc. Natl. Acad. Sci. U.S.A.* 85:5279–5281.

PONS, T. P., P. E. GARRAGHTY, A. K. OMMAYA, J. H. KAAS, E. TAUB, and M. MISHKIN, 1991. Massive cortical reorganization after sensory deafferentation in adult macaques. *Science* 252:1857–1860.

PONS, T. P., J. T. WALL, P. E. GARRAGHTY, C. G. CUSICK, and J. H. KAAS, 1987. Consistent features of the representation of the hand in area 3b of macaque monkeys. *Somatosens. Mot. Res.* 4:309–331.

RAJAN, R., D. R. F. IRVINE, L. Z. WISE, and P. HEIL, 1993. Effect of unilateral partial cochlear lesions in adult cats on the representation of lesioned and unlesioned cochleas in primary auditory cortex. *J. Comp. Neurol.* 338:17–49.

RAMACHANDRAN, V. S., 1993. Behavioral and magnetoencephalographic correlates of plasticity in the adult brain. *Proc. Natl. Acad. Sci. U.S.A.* 90:10413–10420.

RAMACHANDRAN, V. S., D. ROGERS-RAMACHANDRAN, and M. STEWART, 1992. Perceptual correlates of massive cortical reorganization. *Science* 258:1159–1160.

RASMUSSON, D. D., 1982. Reorganization of raccoon somatosensory cortex following removal of the fifth digit. *J. Comp. Neurol.* 205:313–326.

RASMUSSON, D., 1996. Changes in the organization of the ventroposterior lateral thalamic nucleus after digit removal in adult raccoon. *J. Comp. Neurol.* 364:92–103.

RASMUSSON, D. D., D. F. LOUW, and S. A. NORTHGRAVE, 1993. The immediate effects of peripheral denervation on inhibitory mechanisms in the somatosensory thalamus. *Somatosens. Mot. Res.* 10:69–80.

RASMUSSON, D., and B. G. TURNBULL, 1983. Immediate effects of digit amputation on S1 cortex in raccoon: Unmasking of inhibitory fields. *Brain Res.* 288:368–370.

RAUSCHECKER, J. P., 1991. Mechanisms of visual plasticity: Hebb synapses, NMDA receptors, and beyond. *Physiol. Rev.* 71:587–615.

ROBERTSON, D., and D. R. F. IRVINE, 1989. Plasticity of frequency organization in auditory cortex of guinea pigs with partial unilateral deafness. *J. Comp. Neurol.* 282:456–471.

SANES, J. N., S. SUNER, and J. P. DONOGHUE, 1990. Dynamic organization of primary motor cortex output to target muscles in adult rats. I. Long-term patterns of reorganization following motor or mixed nerve lesions. *Exp. Brain Res.* 79: 479–491.

SCHIEBER, M. H., and R. K. DEUEL, 1997. Primary motor cortex reorganization in a long-term monkey amputee. *Somatosens. Mot. Res.* 14:157–167.

SCHWAB, M. E., 1996. Bridging the gap in spinal cord regeneration. *Nature Medicine* 2:276.

SCHWABER, M. K., P. E. GARRAGHTY, and J. H. KAAS, 1993. Neuroplasticity of the adult primate auditory cortex following cochlear hearing loss. *Am. J. Otol.* 14:252–258.

SILVA, A. C., S. K. RASEY, X. WU, and J. T. WALL, 1996. Initial cortical reactions to injury of the median and radial nerves to the hands of adult primates. *J. Comp. Neurol.* 366:700–716.

SNOW, P. J., and P. WILSON, 1991. Plasticity in the somatosensory system of developing and mature mammals. *Progress in Sensory Physiology*, vol. 2. New York: Springer-Verlag.

WALL, J. T., and C. G. CUSICK, 1984. Cutaneous responsiveness in primary somatosensory S-I hindpaw cortex before and after partial hindpaw deafferentation in adult rats. *J. Neurosci.* 4:1499–1515.

WALL, J. T., D. J. FELLEMAN, and J. H. KAAS, 1983. Recovery of normal topography in the somatosensory cortex of monkeys after nerve crush and regeneration. *Science* 221:771–773.

WALL, P. D., 1977. The presence of ineffective synapses and the circumstances which unmask them. *Philos. Trans. R. Soc. Lond. Biol.* 278:361–372.

WEINBERGER, N. W., 1995. Dynamic regulation of receptive fields and maps in the adult sensory cortex. *Annu. Rev. Neurosci.* 18:129–158.

WELKER, E., and H. VAN DER LOOS, 1986. Quantitative correlation between barrel-field size and the sensory denervation of the whiskerpad: A comparative study in six strains of mice bred for different patterns of mystacial vibrissae. *J. Neurosci.* 6:2117–2133.

XING, J., and G. L. GERSTEIN, 1996. Networks with lateral connectivity. I. Dynamic properties mediated by the balance of intrinsic excitation and inhibition. *J. Neurophysiol.* 75:184–199.

XU, J., and J. T. WALL, 1997. Rapid changes in brainstem maps of adult primates after peripheral injury. *Brain Res.* 774:221–215.

YAMASAKI, D. S., and R. W. WURTZ, 1991. Recovery of function after lesions in the superior temporal sulcus in the monkey. *J. Neurophysiol.* 66:651–673.

YANG, T. T., C. C. GALLEN, V. S. RAMACHANDRAN, S. COBB, B. J. SCHWARTZ, and F. E. BLOOM, 1994. Noninvasive detection of cerebral plasticity in adult human somatosensory cortex. *NeuroReport* 5:701–704.

Z'GRAGGEN, W. J., G. A. S. METZ, G. L. KARTJE, M. THALLMAN, and M. E. SCHWAB, 1998. Functional recovery and enhanced corticofugal plasticity after unilateral pyramidal tract lesion and blockage of myelin-associated neurite growth inhibitors in adult rats. *J. Neurosci.* 18:4744–4757.

16 Cerebral Cortical Plasticity: Perception and Skill Acquisition

GREGG H. RECANZONE

ABSTRACT Cerebral cortical plasticity has been demonstrated in a variety of different mammals, following a number of different peripheral and central nervous system manipulations. The reorganization of cortical representations has been implicated in the ability to acquire perceptual and motor skills throughout normal life. This chapter presents evidence from a variety of studies which indicates that cortical plasticity occurs in normal, intact animals and humans, and that these changes in representations are correlated with changes in both motor skills and sensory perceptions.

One of the central goals in neuroscience, particularly in cognitive neuroscience, is to determine the neuronal mechanisms that generate perceptions. Very little is known about how action potentials transmitted throughout the nervous system allow individuals to perceive the complex world around them, to compare this representation of the world to past experience, and to initiate behaviors to achieve goals (e.g., eating, drinking, rest, lively conversation). Although both animal and human studies indicate that the cerebral cortex is integral in processing complex stimuli, very little is known of this structure beyond the presumed relevance of particular areas for specific functions. Although much knowledge has been gained over the past decades on how the individual neurons in a limited number of cortical areas respond to different stimuli, it is still unclear how these responses participate in perception.

While it may be agreed by many that the cerebral cortex is necessary for some perceptions, there is less consensus on how the cerebral cortex is actually functioning to create these perceptions. Further, one of the basic tenets of psychological studies since the late 1800s has been that individuals will improve at virtually any task with continued practice. It was presumed by James (1890) that this improvement in performance was made possible by a change, or "plasticity," of the "organic materials" of the central nervous system.

GREGG H. RECANZONE Center for Neuroscience and Section of Neurobiology, Physiology, and Behavior, University of California at Davis, Calif.

The first real insights into how such changes could be manifest in the cerebral cortex came from studies examining the effects of peripheral nerve injuries on cortical "maps," or representations of the sensory surface, in adult mammals (see Kaas, 1991, and chapter 15). The term *plasticity* is used to describe this capacity to change cortical representations in adults. In such studies denervation, or extensive behavioral use of a restricted sensory surface, results in a change in the central representation of that sensory surface. These results are consistent with the earliest reports of cerebral cortical function performed at the turn of the 20th century by Sir Charles Sherrington and colleagues. Their studies of the motor cortex of monkeys and great apes indicated that movement representations in the motor cortex could be altered over the course of several minutes, and that this effect was reversible (Graham Brown and Sherrington, 1912).

Several other studies have shown that cortical representations most likely reflect the stimulus history of the sensory surface being represented. For example, the cortical representation of the ventral body surface is larger in nursing rat mothers than in non-nursing female rats (Xerri, Stern, and Merzenich, 1994). The selective stimulation of two whiskers either experimentally (DeLacour, Houcine, and Talbi, 1987) or by trimming all but two adjacent whiskers (Armstrong-James, Diamond, and Ebner, 1994) results in many more neurons within the somatosensory cortex responding to both of the two whiskers. In primates, surgical fusion of two digits results in a zone of cortex in area 3b in which neurons have receptive fields that cross the suture line and respond to parts of both fused digits, in contrast to the normal situation where 3b neurons rarely, if ever, respond to stimulation of two digits (Allard et al., 1991; see also Merzenich et al., 1987). Finally, Jenkins and colleagues (1990) showed that training monkeys to attend to stimulation on the tip of one or two fingers results in an increased representation of the stimulated fingertips compared to the unstimulated fingers. Similar kinds of short- and long-term plasticity have been observed in the visual cortex as well as in human sub-