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"Reorganization of Cortical Representations of the Hand Following Alterations of Skin Inputs Induced by Nerve Injury, Skin Island Transfers, and Experience"

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Reorganization of Cortical Representations of the Hand Following Alterations of Skin Inputs Induced by Nerve Injury, Skin Island Transfers, and Experience

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ABSTRACT: Tactile experiences remodel the central nervous system representations of the body surface. The results of assessments of ten peripheral manipulations that reveal different aspects of representational plasticity are reviewed: (1) chronic peripheral denervation; (2) surgical amputation; (3) digital syndactyly and its natural behavioral equivalents; (4) peripheral nerve crush with reinnervation; (5) peripheral nerve transection and repair, with reinnervation; (6) denervation of very large skin surfaces, for very long times; (7) electrical stimulation of large-fiber afferents in the median nerve, simulating electroacupuncture; (8) implantation of always-innervated island pedicle flaps; (9) behavioral training with locationally invariant stimuli; and (10) behavioral training with moving stimuli. Focus is on the changes recorded in a primary somatosensory cortical field, area 3b, following these ten manipulations, in adult monkeys. On the basis of these findings, the following are discussed: (1) how altered schedules of activity from the skin contribute to cortical representational remodeling; (2) other factors that influence the representational remodeling; (3) where the remodeling actually occurs; and (4) some implications of these findings for sensory rehabilitation.

Experiments conducted principally over the past decade have revealed that the central nervous system representations of the body surface are remodeled by tactile experiences, throughout life.[42,52,53] The central somatosensory system "plasticity" that underlies these use-dependent changes in brain "representations" of the skin was first indicated by studies of the somatosensory systems of cats and monkeys that had undergone limited peripheral skin deafferentations.[34,41,46,53,84] Following peripheral nerve transections after which regeneration was not allowed,[35,41,48,49,56] or after dorsal rhizotomies[17] or central tract lesions,[86] it was demonstrated that large zones of the dorsal column nuclei, thalamus, and cortex, deprived of their principal driving inputs by these lesions, were progressively occupied by almost equally powerful inputs from the surrounding, intact skin.

As our understanding of the nature and bases of representational remodeling in the somatosensory system developed, the consequences of other peripheral input manipulations were assessed. Those other manipulations have included: (1) surgical amputation[37,51,68]; (2) surgical syndactyly and its natural behavioral equivalents[2,10]; (3) nerve crush, with skin reinnervation[6,87]; (4) nerve transection and repair, with skin reinnervation[1,45,84,89]; (5) chronic skin denervation covering very large skin surfaces, over very long time periods[65]; (6) electrical stimulation of large-diameter axons of peripheral cutaneous nerves simulating the peripheral cutaneous nerve activity generated by episodes of electroacupuncture[69]; (7) implantation of translocated, neurovascular island pedicle flaps[43,44,52,53]; (8) behavioral training in which stimuli were applied to constant skin loci[70,73,74]; and (9) behavioral training in which stimuli move across the skin.[33]

In this review, we briefly summarize the changes recorded in a primary somatosensory cortical field, area 3b, following these ten peripheral manipulations. As these findings are summarized, it should be remembered that changes recorded in a cortical map will reflect the representational remodeling occurring at the two subcortical relay nuclei on the somatosensory system mainline—i.e., within the dorsal column nuclei and in the ventrolateral division of the ventrobasal thalamus—as well as the changes contributed by cortical plasticity itself. To simplify the depiction of the complex findings of many experiments conducted in rodents, chiropterans, carnivores, and primates, we focus on studies of the plasticity of the cortical area 3b representations of the surfaces of the hands of adult monkeys. This cortical field is the true "primary" somatosensory cortical field in monkeys[47,58] and is the most robustly excited, orderly, and topographically consistent of the several body surface representations in the primate cortex.

After describing the basic neurologic and perceptual changes induced by these various peripheral manipulations, we briefly consider: (1) the features of the new schedules of activity from the skin that contributed to them; (2) several other factors that can

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influence representational remodeling; (3) probable somatosensory system levels contributing to different aspects of representational remodeling; and (4) some implications of these findings for sensory rehabilitation.

NORMAL ORGANIZATION OF THE REPRESENTATION OF THE HAND IN AREA 3b IN ADULT MONKEYS

Before describing the consequences of peripheral input manipulations on the cortical area 3b "map" of the hand in monkeys, it is important to understand the way that the surfaces of the hand are normally represented within it. The pattern of representation of the hand in this cortical field has been defined in our experiments by introducing several hundred parallel recording microelectrode penetrations in a fine grid covering the area 3b hand representation zone (Fig. 1 A). Two New World monkey species, the owl monkey (*Aotus*) and the squirrel monkey (*Saimiri*) have been most often employed as models in these experiments, in part because their central sulci do not extend lateralward into the hand sector of the anterior parietal somatosensory fields (S1), thus facilitating its detailed mapping. In these two primate species, the hand zone of cortical area 3b is roughly 8 to 14 mm^2.

For defining a "map" of the hand, the skin surfaces effective for exciting neurons are determined for cortical neurons within a given cortical layer by carefully exploring the skin with fine mechanical probes, or by the use of press-calibrated von Frey hairs. The *cortical receptive field* defined at each sampled site is the skin surface that, when stimulated mechanically, excites one or more cortical neuron(s) at that location. Typical cortical receptive fields are diagrammed in the hand drawing in Figure 1 C. Receptive fields recorded at nearby sampled locations overlap with one another.[66] They normally do not overlap when cortical samples are derived for skin locations more than about 500–600 microns apart; with closer samples, overlap is roughly proportional to the distance between samples.[77] From any fine row of sample sites, receptive fields shift continuously and systematically across the hand (Fig. 1 B and C). *There is a single, simple representation of the glabrous surfaces of the hand* (and most of the remainder of the body surface) *in area 3b.*

From these fine-grained microelectrode penetration neuronal response samples, a "map" of the functional surfaces of the hand can be constructed. Such a map, shown in highly diagrammatic form, is illustrated in Figure 1 B. There, outlined areas are the cortical territories representing different designated hand surfaces, e.g., the areas over which cortical receptive fields were all located on individual digits, or on the palm. The details of the hand representations are very different in different individual monkeys,[42,50] but the overall pattern of representation in normal adults is reasonably constant. Fields along the lateral border of the area 3b hand zone (downward in Fig. 1 B) abut the face representation. There, receptive fields are arrayed along the radial margin of the hand. Progressing medialward (upward in Fig. 1 B), successively recorded receptive fields move across the volar, glabrous surfaces of the fingers, from radial digit 1 in digital progression to ulnar digit 5, or, at a more posterior level, across the radial-to-ulnar dimension of the palmar pads.

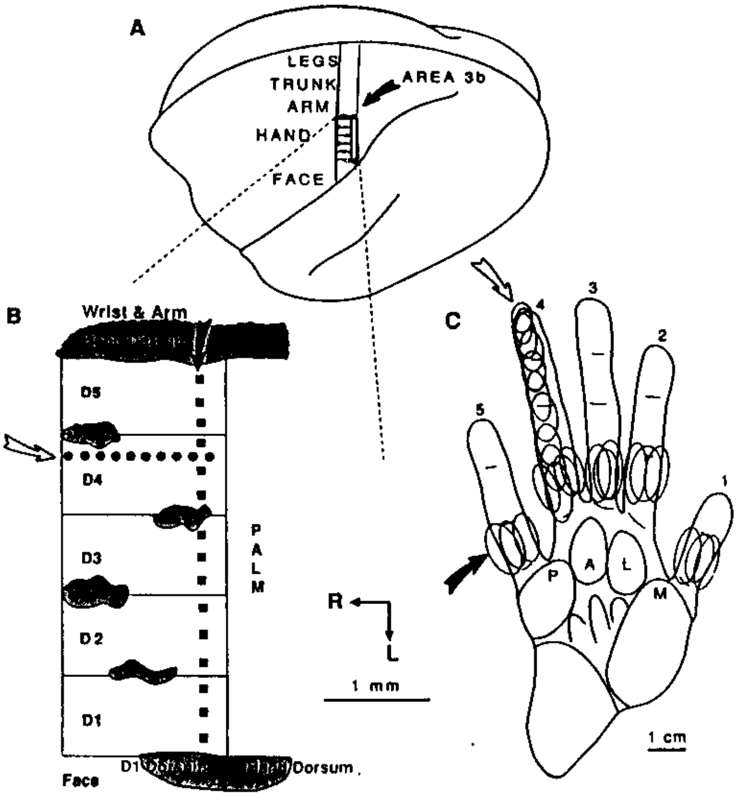


*FIGURE 1. Normal pattern of representation of the surfaces of the hand within the true primary somatosensory cortex, area 3b, depicted for the brain of a New World owl monkey. In this species, the representation of the hand in this cortical area is completely exposed on the lateral surface of the cortex (**A**); in most primates, including man, it is buried in a deep (central) sulcus. In this lateral view of the left cerebral hemisphere of the owl monkey, the anterior pole is to the left. There is a complete, orderly representation of the volar glabrous surfaces of the hand in area 3b, reconstructed diagrammatically in **B**. There, outlined areas represent cortical zones in which neurons responded to stimulation on indicated digits (D1 to D5), or on the pads of the palm. The zones of representation of dorsal surfaces are shaded. These patches representing surfaces on the backs of the hand and digits flank the volar glabrous digit zone, and are insinuated between digit representations. Discontinuities sharply divide the representations of this hairy skin with the volar glabrous skin, and sharply divide the territories of representation of individual fingers. Typical cortical receptive fields—the skin surfaces effective for exciting cortical neurons at given loci—are shown on the hand drawing (**C**). Receptive fields shift continuously for neuronal responses recorded in orderly sampling sequences across this field (**B** and **C**). Receptive fields derived at nearby recording sites significantly overlap one another. Based on results from Merzenich et al.*[47,50]

The skin under the nails at the extreme digit tips is represented along the rostral border of the hand zone of area 3b. For sample sites shifting caudalward, successively defined receptive fields shift progressively proximalward down the digits (Fig. 1), then down the palm toward the wrist. The dorsal hairy surfaces of the hand are represented in highly variable and unpredictable patches (shaded in Fig. 1) that lie along the lateral, medial, and rostral margins of the glabrous skin representation, or are insinuated between the glabrous zones of representation of adjacent digits. The hand dorsum is normally represented incompletely in area 3b, with neurons commonly responding to stimulation, in different monkeys, of about one-fifth to about two-thirds of the surfaces of the back of the hand.[50]

There are three interesting kinds of representational discontinuity in the hand representation of area 3b. First, there is a discontinuous pattern of representation of the volar, glabrous hand surfaces and the dorsal, hairy surfaces. As described above, receptive fields normally overlap on the skin when samples are derived from nearby cortical locations. However, neurons do not usually have receptive fields that extend from the glabrous to the hairy surfaces of the skin; as a rule, they respond at least predominantly to stimulation on one or the other surface, but not strongly to both.

Second, glabrous surfaces of individual fingers are discontinuously represented. Neurons in this cortical field relatively infrequently respond to glabrous stimulation of more than one digit; as a rule, even for sample sites very near a line of representational discontinuity, neurons respond predominantly to one or the other finger. With a short step across that line, with rare exception, neurons respond exclusively to stimulation of the glabrous surfaces of the adjacent digit.

Third, the representation of the palm is split down its midline, with the skin along the facing surfaces of the thenar and hypothenar eminences represented in widely separated cortical zones.

Features of representation of the hand in area 3b to remember in the following discussion are: (1) its orderly, topographic representations; (2) the patches of hand and digit dorsa on the margins of the glabrous hand representation, and insinuated between volar glabrous finger representations, altogether representing only a fragment of the dorsal hairy digit and hand surfaces; (3) the shifted-overlap organization, by which any given spot on the skin is usually represented by receptive fields of neurons over a distance of about 500–600 microns; and (4) its representational discontinuities separating the area 3b zones of representation of individual fingers, and segregating the representations of the dorsal hairy and volar glabrous surfaces of the skin.

CHANGES IN THE CORTICAL AREA 3b REPRESENTATION OF THE HAND INDUCED BY PERIPHERAL ALTERATIONS OF TACTILE INPUTS

Chronic Peripheral Denervation

Cortical representational changes. If a digital cutaneous nerve is cut and its regeneration prevented, its cortical area 3b representation progressively reorganizes to occupy the zone now deprived of its main driving input. For example, if the median nerve is severed, its cortical territory is completely occupied within about one week following the lesion (Fig. 2). That occupation begins to emerge immediately after the cut, when large receptive fields representing surfaces on the hand dorsum or the glabrous skin of the radial aspect of the ulnar nerve skin appear.[8,14,49] However, this initially emerging input is crude and incomplete, emergent receptive fields are abnormally large, and they overlap one another over abnormally great distances.[49] Several days later, when the former-median-nerve cortical zone is fully occupied by "new" driving inputs, receptive fields have shrunken

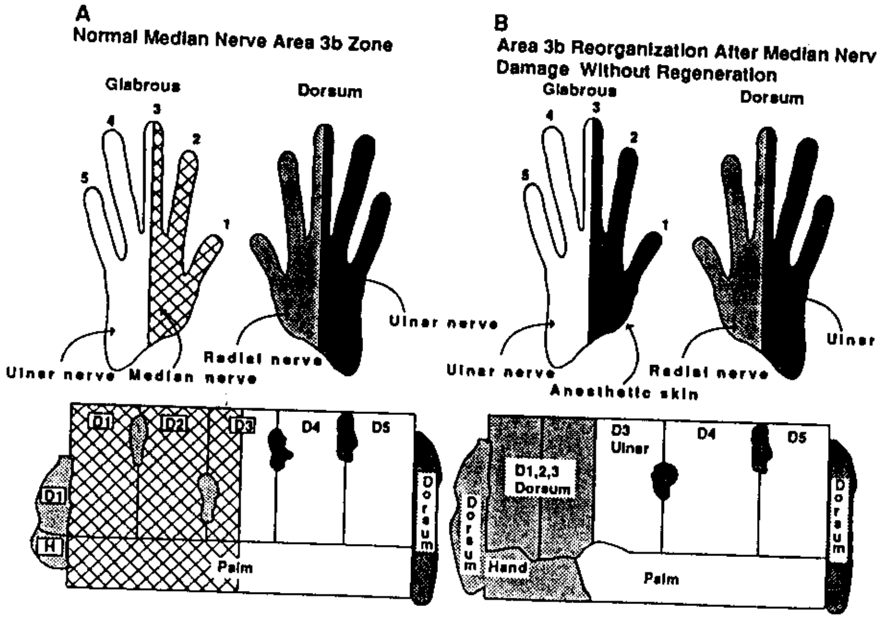


*FIGURE 2. Cortical representational changes (**B**) recorded a month or longer after the median nerve is cut, with regeneration not permitted. After cortical map reorganization, neurons all across the former median nerve zone (shown in **A**) are excited by inputs from surrounding skin nerves (**B**, lower right). Occupying inputs are from the dorsal hand and fingers innervated by the radial nerve, and by the glabrous skin of digit 3 and the central palm zone innervated by the ulnar nerve. Based on results from Merzenich et al.*[48,49]

and their overlaps have been reduced. However, receptive fields and cortical topographies are subject to further great refinement over subsequent days. Within two or three or four weeks, the topography of representation of the "new" inputs in this zone is as refined as was the topography of the original representation of the median nerve skin, and receptive field overlap as a function of distance is once again indistinguishable from normal.[21,49]

After it loses its median nerve inputs, what skin inputs occupy this several mm^2 area 3b zone? There are three main sources (Fig. 2): (1) The representation of the radial dorsal hairy hand enlarges and comes to excite neurons located far medialward from its normal zone of representation. (2) A beautiful, complete topographic representation of the dorsal hairy fingers emerges, almost equal in detail to the representation of the glabrous digital skin that it supplanted. No equivalently detailed representation of the digit dorsi has ever been recorded in a normal hand map in cortical area 3b in these monkeys. (3) The representation of the glabrous surfaces of D3 and the central aspect of the glabrous palm innervated by the ulnar nerve expand lateralward, to occupy a 3b sector two or three times larger than normal.

Parallel human perceptual changes. Perceptual changes for the skin adjacent to a denervated skin zone have not been adequately documented. More complete descriptions come from studies of amputation cases, as briefly outlined below.

Amputation

Cortical representational changes. What happens if the inputs from the backs of the fingers are not allowed to occupy an area 3b zone deprived of its effective glabrous digit inputs? That question is important because several lines of evidence suggest that there might always be usually suppressed representations of the backs of the digits embedded in the glabrous digit representational part of area 3b.[46,49] It was answered in experiments in which digital cutaneous nerves were cut and tied, and one or two digits subsequently surgically amputated. While such experiments have been conducted in both raccoons[37,68] and monkeys,[51] with important findings from both models, results and interpretations differs somewhat; in this brief review, we focus on the findings in primates.

Immediately following digit amputation, receptive fields representing surrounding skin surfaces greatly enlarge and can extend over wide regions of adjacent digits or the subjacent palm (Allard TA and Merzenich MM, unpublished observations, 1988–1993).[8,14,49] Although our data describing the time course of change are very limited, instances have been recorded in which such large fields have been recorded immediately after amputation within the "deprived" zone; responses at other sites in this zone were temporarily rendered silent, with no cutaneous response emerging when the animal woke up from surgical anesthesia.

Several weeks later in a monkey model, most or all of the area formerly representing the now-missing digit is occupied by new inputs from the adjacent fingers and subadjacent palm[51] (Fig. 3). To accomplish this change, receptive fields with initially large extents had greatly shrunken; and responses have emerged in cortical zones that were initially rendered silent by the amputation.

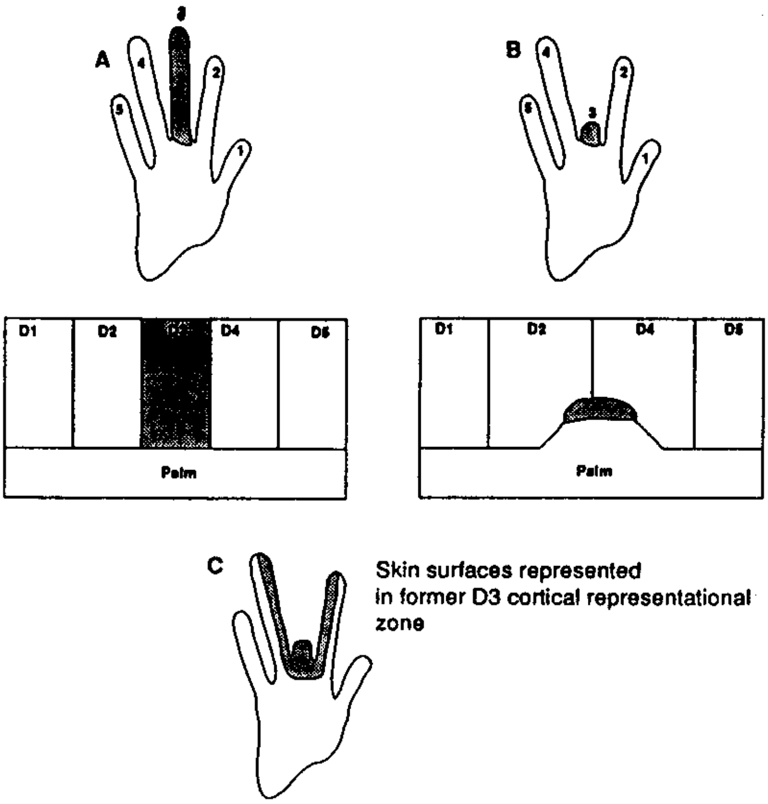
The occupation of this zone by surrounding inputs was best described as a *topographic representational expansion*. After reorganization, part of the surfaces of the surrounding skin were represented *only* within the cortical territory formerly representing the now-missing digit(s). With expansion, receptive fields were smaller than normal, in approximate proportion to the degree of representational expansion. *As a consequence, these skin surfaces were now represented in finer spatial grain.*

With expansion of the representations of digits bordering the now-missing fingers, they ultimately came together representationally at a new line in the cortex (Fig. 3). There, they formed a new discontinuity, commonly at a location where no representational discontinuity had existed before.

Parallel human perceptual changes. In humans suffering limb amputations, a progressive perceptual shortening of the phantom limb ("telescoping") occurs in the weeks following the amputation.[30] *Concomitantly and proportionately,* there are progressive changes in tactile spatial acuity and sensitivity on the limb stump.[25,26,36] The time course and nature of these changes parallel those of plastic changes in cortical maps, and are plausibly due to them.[36,51] That is, as originally hypothesized by Teuber and colleagues,[79] these perceptual changes for the stump skin may be attributable to the expansion of the cortical representation into the zone formerly representing the now-missing digit. With its representational expansion, the skin surfaces of the stump are represented in finer spatial grain.

As the phantom limb perceptually telescopes, some individuals have very clear and sharply localized "ghost" sensations evoked by point stimulation on the stump. That is, stump stimulation is correctly located, but point stimulation can also evoke a second, equally sharp sensation that is located to the phantom extremity. These referred second sensations can be mapped on the stump skin, and are topographically related to it.[13,36] That finding is consistent with the hypothesis that the cortical representation of the stump skin in these individuals has topographically expanded to the extent that it now directly overlies the former representation of the skin of the extremity of the now-missing limb.

Two contemporary[12] studies further reinforce this conclusion. First, in a fascinating human case, Craig[12] has shown that limb telescoping can also result from a heavy schedule of stimulation of the forearm that renders the arm insensate. After a period of days or weeks of strong response adaptation, the arm was perceived as foreshortening by the length of the forearm, with sensations on the hand and upper arm correctly localized and normally useful through the period of induction of this change. However, with release of the adapting skin stimulation, the forearm



Skin surfaces represented in former D3 cortical representational zone

FIGURE 3. *Reorganization of area 3b recorded a month or longer after the digital cutaneous nerves of the third (long) finger were cut and tied, and the digit surgically amputated at the base (***B***). The zone of cortex formerly representing the now-missing finger (***A***) comes to be occupied by expanded inputs representing the adjacent digits and subjacent palm (***B*** *and* ***C***). Those expanded representational zones (1) have smaller receptive fields and (2) form a new discontinuity between the formerly widely separated area 3b representations of the radial and ulnar surfaces of digits 4 and 2. Based on results from Merzenich et al.*[51]

again recovered its sensibility. Now, stimuli were correctly located on it; but second "ghost" sensations were also evoked on the surfaces of the proximal hand or upper arm. Similarly, forearm "ghosts" were evoked by proximal hand or upper arm stimulation. With either stimulation format, both correctly located and "ghost" sensations could be mapped topographically, relative to one another.

The cortical reorganization hypothesis most consistent with these remarkable observations is that in the absence of effective forearm inputs, the cortical representations of the upper arm and proximal hand expanded topographically to occupy the zone formerly representing the silenced forearm skin. Consistent with that interpretation, with recovery of the sensibility of the forearm skin, the underlying representations of hand and upper arm appeared to march out from under the forearm representation, i.e., second, referred sensations moved progressively day by day until no overlap was indicated, about two weeks later.[12]

In a second interesting study, Ramachandran and colleagues[67] have demonstrated that sensations can be evoked on the phantom hand by stimulation of the face within days after arm amputation. Again, that finding was consistent with a relatively rapid, partial occupation of the representation of the distal aspect of the missing limb with effective inputs from the face. Because the inputs from the hand and face are strictly anatomically segregated at all subcortical levels, this effect is presumably accounted for by cortical representational remodeling.

It should also be noted that the degree of telescoping, the development of high acuity on the stump, and the nature of the image of the stump itself are all significantly influenced by stump use.[36]

Digital Syndactyly and Its Natural Behavioral Equivalents

Cortical representational changes. What accounts for the emergence of representational discontinuities between digits? They are not likely accounted for on an anatomic basis, because anatomic inputs projecting from the fingers to the cortex are not segregated into narrow bands corresponding to the extents of represented digits, but spread relatively widely, several finger widths across the cortical horizon.[34,53,76,92] Moreover, when afferent inputs from two digits formerly represented far apart come to abut each other representationally after digit amputation, they form a new, sharp area 3b discontinuity, in a location where none was seen before. Furthermore, as described below, the sharp representational boundaries between fingers can be shifted hundreds of microns across the cortex by delivering heavy stimulation to just one or two of them. We hypothesized[2,10] that the time coincidence of inputs might be responsible for a functional segregation of effective finger inputs. By that hypothesis, fingers are represented discontinuously because inputs delivered into the somatosensory system from adjacent digits generate substantially nonsimultaneous inputs from them. If that explains the basis of the brain creating separate finger representations, then they should be eliminated by creating a digital syndactyly. With syndactyly, by which the glabrous and hairy surfaces of adjacent digits are surgically fused after cutting the skin down the mid-

5

lateral line of the digits, the skin along the suture line formerly on separated digits is now invariably stimulated nearly simultaneously in time. On that basis, the discontinuity between digit representations should disappear.

That is just what happens (Fig. 4). After a period of syndactyly, two fused digits come to be represented just like any other single digit. That is, receptive fields progress in a shifting overlap sequence all across the fused digit representational sector, with many receptive fields spanning the syndactyly scar line.

At the end of these experiments, syndactylies were surgically corrected and the cortices immediately remapped. Now, across the same wide cortical zone, sampled neurons had two receptive fields, one on each of the two adjacent digits. Again, the recording of two-digit glabrous receptive fields was an unusual occurrence in normal cortex. Their recording in this control experiment confirmed that the highly anomalous representations recorded after a period of digital syndactyly were accounted for by representational remodeling in the central nervous system.

If this interpretation is correct, we should be able to break down the independent representations of fingers by using natural stimuli that simultaneously engage the surfaces of more than one digit. That has been accomplished by training monkeys to make distinctions about a long bar stimulus that simultaneously strikes the surfaces of three fingers. After such training, a wide swath of neurons was found that had receptive fields with components on either two adjacent, or on all three fingers (Wang X, Merzenich M, and Jenkins W, unpublished observations, 1992–1993). Again, two-digit receptive fields are infrequently recorded and three-digit receptive fields are virtually never normally recorded within the heart of cortical area 3b in normal monkeys. Their emergence in these experiments reveal that cortical discontinuities are functional, afferent input time-based constructs.

Parallel human perceptual changes. Benedetti[5] simulated the amputation of a finger by having subjects wear bandages covering a digit over a six-month period. In time, the subjects had perceptual illusions that normally apply only to objects manipulated by adjacent fingers. Similarly, he demonstrated that double-image phenomena normally arising by manipulating objects with the digits crossed disappear when two adjacent fingers are bound in a crossed position over a period of weeks, consistent with a central representational remodeling now permitting appropriate perceptual integration from what were formerly the far sides of adjacent digits.[4] Both sets of observations were interpreted in terms of the establishment of new representational relationships between removed skin surfaces (the creation of new representational discontinuities?) on the basis of experience.

Heavy hand use involving nearly simultaneous stimulation of fingers can result in a loss of independent digit control. In experience-induced "writer's cramp" or "focal dystonia," rapidly alternating finger movements can no longer be performed.[59,75] Although this condition likely arises from a change in the pattern of representation of muscle afferent inputs and not just from skin inputs, these digit fusion and simultaneous stimulation studies suggest a likely origin: Nearly simultaneous stimulation of adjacent digits (or excitation of muscle afferents) on a heavy schedule destroy their normally discontinuous representations—and, thereby, their independent cortical representations and categorical identities.

Peripheral Nerve Crush with Reinnervation

Cortical representational changes. What are the representational consequences of crushing, then waiting for regeneration of a large peripheral cutaneous nerve such as the median nerve? If the crush injury occurs in the proximal hand or in the arm, we know that the cortical zone representing the median nerve will be entirely occupied by inputs from surrounding skin regions before peripheral regeneration can occur. Somewhat surprisingly, there is little evidence of this representational turmoil after nerve regeneration. The cortical representation of the median nerve skin after regeneration is not substantially different from the normal representation recorded under

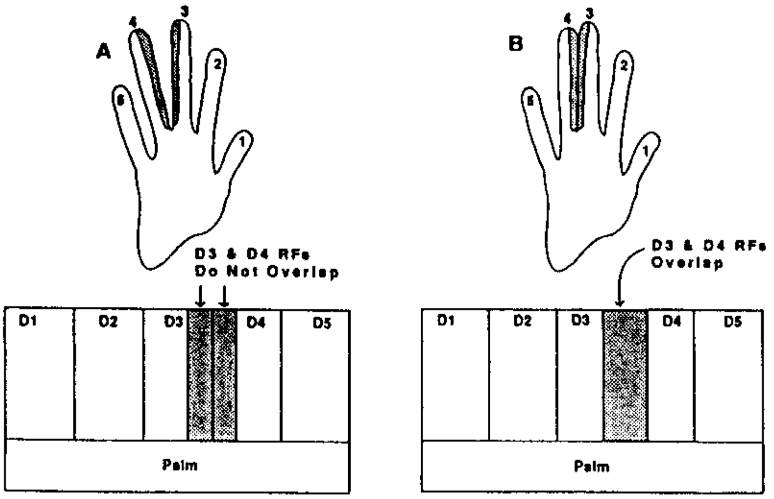


*FIGURE 4. Remodeling of cortical area 3b, after a one-month or longer period of digital syndactyly (**B**). In the normal condition (**A**), representations of digits along the zones of representations of bordering skin surfaces do not significantly overlap in the cortex: As a rule, on either side of a sharp border, neurons respond to stimulation of one or another of the two fingers. After a period of syndactyly (**B**), neurons all across a broad cortical zone have receptive fields (RFs) that span the syndactyly suture line—that is, in contradistinction to the normal case, have components on both fingers. This effect is not due to changes in the skin itself, because these novel receptive fields persist after the digits are reseparated. Based on results from Allard et al.[2]*

6

sterile conditions in the same animals prior to the crush injury[6,87] (Fig. 5).

Parallel human perceptual changes. Consistent with cortical plasticity findings, no permanent localization problem, paresthesia, or mislocalization usually ensues after recovery from crush injuries. This apparently occurs because regenerating axons follow their old Schwann cell tubes—which survive crush injuries—back to their prior skin locations, thereby reestablishing the approximate original afferent input anatomy.

Peripheral Nerve Transection and Repair, with Reinnervation

Cortical representational changes. If a peripheral nerve is cut and then repaired, a radically different cortical remodeling scenario is recorded. Peripheral nerve transections result in a shuffling of skin addresses with respect to central nervous system addresses. In our studied monkeys,[1] as in humans with peripheral nerve repairs,[27] peripheral nerve branches do not retain a representational topography. Cutaneous receptive fields of adjacent fibers jump in almost random order across the skin field of the nerve, and any small nerve bundle in the zone of nerve reconnection contains skin inputs from all across the skin field of the nerve, rather than across a limited discrete skin area as in the normal case.

What does the central somatosensory system do with this shuffled input? On the basis of anatomy alone, we might expect that all cortical receptive fields would be very large. In the normal system, adjacent neurons represent adjacent skin loci; hundreds of neurons operate cooperatively to generate small cortical receptive fields. If the skin inputs to those adjacent neurons are shuffled, all cortical neurons should respond roughly to most or all of the median nerve skin field.

What changes are actually recorded? First (Fig. 6), the median nerve does not recapture all of its original territory.[63,89] Long after regeneration is complete, a third or a fourth of it is found to still be occupied by expanded representations of surrounding skin, reflecting a residual consequence of those representational changes that occurred before peripheral nerve regeneration could occur. In contrast to the crush experiment, the regenerated median nerve is a less effective competitor against the usurping inputs from surrounding skin regions. We believe (and studies of cortical networks support the conclusion) that this is because the shuffled inputs provide a far less powerfully coherent input. In the normal condition, where inputs to any given cortical locus are from nearby skin locations, they are excited more nearly simultaneously on heavy schedules than when inputs come from locations scattered all across the median hand surfaces.

Second, contrary to anatomic expectations, receptive fields at most sampled sites are of roughly normal size.

Third, the majority of sampled neurons have more than one receptive field. Many have one receptive field on the far radial aspect of the always-innervated ulnar nerve skin, and one or more others on the median nerve skin. Many others have two or three or more receptive fields scattered across different locations on the median nerve skin.

Fourth, any given functional skin surface—e.g., the thumb (Fig. 6), a segment of a finger, or a palmar pad—is represented across several small separated patches in the regenerated median nerve skin zone, rather than in a single large continuous zone, as is normally seen.

Fifth, despite the existence of multiple receptive fields and a fractured representation of any given functional skin surface, there is a remarkable reestablished representational topography within the reorganized median nerve area 3b zone. Moving across the reorganized cortex in any dimension, receptive fields overlap and shift progressively, with that shifting occurring in completely unpredictable directions re the normal topography. When the edges of a representational patch are crossed, a break in topography for that functional skin surface is, of course, recorded; but commonly, other small, simultaneously recorded receptive fields overlying other functional skin surfaces continue to shift progressively across these representational breaks.

How does the somatosensory system create small receptive fields from spatially shuffled inputs? Why

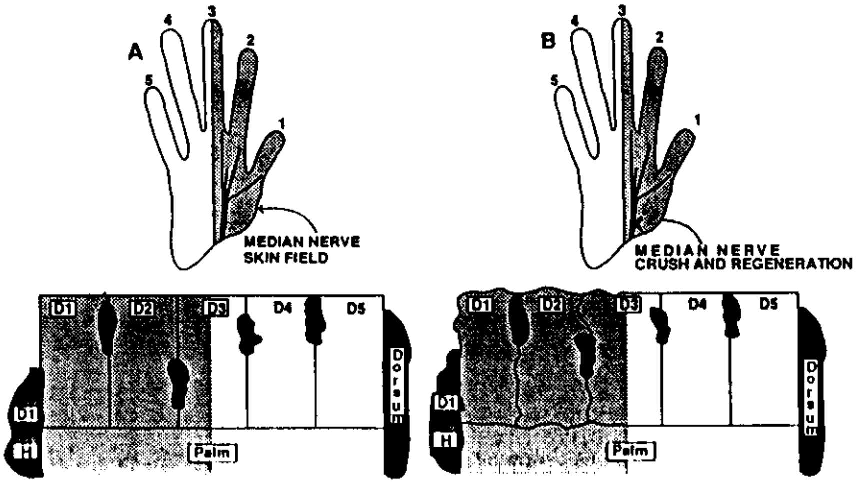


*FIGURE 5. Although small differences in representational detail can be seen, no statistically different change in the area 3b representation (**A**) of the median nerve skin results from regeneration after median nerve crush (**B**). Based on results from Wall et al.[87]*

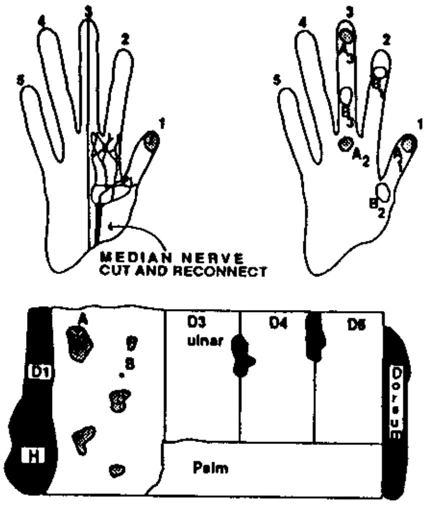


FIGURE 6. Some cortical representational changes recorded after nerve section and repair. The median nerve does not recover all of its original representational territory, as expanded inputs from the ulnar and radial nerve still retain expanded representations of surrounding skin surfaces in the former median nerve zone in area 3b. Functional skin surfaces (the distal thumb segment in this example) are represented in the zone of the regenerated nerve in a series of separated representational islands (light shading). Sampled neurons have small receptive fields, but commonly respond over more than one small skin field; two typical multiple-field examples (sample sites A and B) are shown. Receptive field components are always relatively widely separated on the skin from one another. Based on results from Wall et al.[89] and Allard et al.[1]

does it generate more than one receptive field for most cortical loci? We hypothesized that it must use neural discharge timing information to create the new topography. Resorting requires that central neurons select those specific combinations of shuffled afferent inputs that are excited simultaneously in time when any given, restricted skin locus is stimulated. Interestingly, multiple receptive field components were always found to be separated from one another by significant distances across the fingers and palm. If timing information contributes to making small receptive fields from shuffled inputs, then this mechanism would likely be able to operate only over distances over which inputs have significant correlational relationships. At far distances, inputs delivered from the skin would be essentially temporarily independent. A self-organizing system would have no basis for eliminating distant inputs, and the same selective processes would work to create another small receptive field over those distant skin regions.

If these observations are correctly interpreted, the cortex should be able to create a completely orderly representation of a smaller reinnervated skin surface, if that reinnervated skin surface is small enough to produce appropriately temporally correlatable inputs. To test that conclusion, we repeated nerve transection experiments, in this case tracking changes that followed transection and reconnection of single digital cutaneous nerves. In that model[1]: (1) single-component receptive fields were recorded in the regeneration zone as a rule; and (2) a roughly normal topography was recorded, by which the representation of the denervated/reinnervated half of the finger was aligned with the representation of the other half of the finger.

Parallel human perceptual changes. In adults, ulnar or median nerve repair ultimately results in a correct localization of stimulated sites, but with a common, persistent evocation of one or more additional mislocated "ghost" sensations.[16,28,81] Persistent mislocalizations are consistent with the overlying of inputs from different skin surfaces at a large percentage of area 3b sites in the reorganized median nerve zone. Our results would suggest that these secondary referred sensations would not ordinarily be located on the same functional skin surfaces, but would be separated by minimal distances from stimulated skin spots. They also suggest that referred mislocated ghost sensations should often emerge on the ulnar nerve skin, along its border with the median nerve skin. To our knowledge, neither prediction has yet been tested in humans.

It should be pointed out that the re-establishment of correctly located median skin field stimulation demonstrates that the somatosensory system has the capacity to correct peripheral references, as the central locations of excited neuronal population for stimulation at any median nerve skin locus are very different from the original. The system could presumably also make constructed representations of stimuli across representational discontinuities, because it normally does so, for example, across the discontinuity that splits the palm representation into two separated halves. Limitations in recovery occur in large part because representational reorganization is marked by the creation of overlying representations of skin, which produce complexly confounded three-dimensional representations of felt objects.

In children below the age of 9 or 10 years, recovery from large hand nerve lesions can be complete, as it can be for a small percentage of adults with large hand nerve injuries.[18,39,78] This difference may be explained by the creation of a more orderly representation of the hand after neonatal as compared with adult nerve regeneration.[88] Consistent with the studies of Allard and colleagues,[1] recovery of normal sensibility often occurs in adults following digital nerve repairs.

In older children and in adults, the literature strongly supports the conclusion that sensory uses of reinnervated hand surfaces are strongly facilitated and augmented by a scheduled program of "sensory re-education."[31,38,57,91] Thus, as in most above-described peripheral skin manipulations, there is an experiential contribution to representational changes that clearly contribute to recorded perceptual sequelae.

Skin Denervation of Very Large Skin Surfaces, for Very Long Times

Cortical representational changes. An intriguing cortical mapping experiment has recently been conducted in adult macaque monkeys that had undergone dorsal rhizotomies deafferenting one or both arms many years prior to the derivation of area 3b maps.[65] In these monkeys, the entire cortical zone of representation of the hand and arm—an area roughly 1 cm^2—was found to be occupied by a greatly expanded representation of limited surfaces of the anterior face. These results were surprising because of the great distances over which new occupying inputs were recorded. In this case, they clearly extended well past the limits of anatomic spreads of inputs from given skin surfaces, for the afferent projections from the skin to the cortex.

Parallel human perceptual changes. The phantom limbs of patients with extensive dorsal rhizotomies or brachial plexus injuries do not telescope.[36] The basis for this difference is unclear. For more limited lesions, there is no discernible difference between the cortical plasticity recorded when a nerve is transected, in which case most dorsal root ganglion cells survive, and this condition in which all ganglion cell bodies from a nerve are destroyed by injecting ricin into the body of a nerve.[88] Whatever its explanation, the failure of the phantom limb to perceptually "telescope" after extensive dorsal rhizotomies is consistent with the finding that, despite the fact that the skin of the face "moved" more than a centimeter into the forelimb cortical zone, the trunk representation in these interesting cases did *not* expand.

Very long representational translocations have also been described for proximal limb movements, in patients suffering amputations.[11,19] However, the remarkable several-centimeters-distant functional remodeling recorded in motor cortex in these cases may be attributable to an always-present, usually suppressed, underlying representation of proximal limb movements in the zones predominantly representing distal limb movements, as is suggested by animal experiments.[60]

Electrical Stimulation of Large-fiber Afferents in the Median Nerve, Simulating Electroacupuncture

Cortical representational changes. In a series of experiments conducted in adult cats but not yet in a primate model, we have assessed the consequences of a period of electrical stimulation of the large-fiber afferents of a single peripheral cutaneous nerve.[69] Such stimulation simulating the consequences of an extended period of electroacupuncture delivers perfectly synchronous afferent inputs into the central nervous systems zones of representation of a peripheral cutaneous nerve on a heavy schedule. This stimulation was predicted to result in the creation of abnormally large receptive fields. That result was recorded: Receptive fields in the cortical zone of the median nerve of a cat, after several hours of large-fiber afferent stimulation, were several times larger in area than normal (Fig. 7). However, the interpretation of the origins of this effect were complicated by the fact that receptive-field size changes were not restricted to the skin field of the nerve, but applied to the entire representation of that half of the body surface! In fact, three- to fivefold changes in receptive field sizes were recorded for the entire forepaw and hindpaw representational zones in the homolog of area 3b in the cat, and seven- to >20-fold changes in receptive field sizes were recorded within the arm, trunk, and leg representational zones.

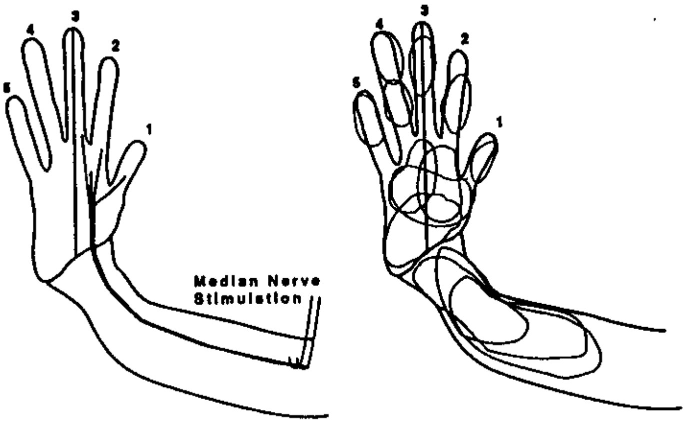


FIGURE 7. Hypothetical receptive fields recorded after area 3b modeling resulting from a several-hour-long period of large-fiber afferent stimulation of the median nerve, simulating an extended period of electroacupuncture. In comparison with the normal case (Fig. 1), receptive fields are enlarged several-to many-fold in extent, with effects of stimulation of one hand nerve not limited to the zone of representation of the stimulated nerve, but applying to all across the body surface ipsilateral to the site of hand nerve stimulation. Note that these experiments have been conducted only in a cat model; these drawings are based on a hypothetical extrapolation of those results to primates. Based on results from Recanzone et al.[69]

Thus, these studies revealed a dramatic consequence of a single, extended period of simulated electropuncture that applied to the entire body surface ipsilateral to the stimulated nerve, and hence, may provide the beginning of an explanation for its referred, distant effects.

The very widespread topographic consequences of this simple manipulation indicated that they might be explained by the parallel engagement of the endogenous opiate system(s) by this heavy schedule of perfectly simultaneous afferent inputs.[69] Consistent with that conclusion, effects of electrically shocking peripheral cutaneous nerves were completely blocked by administration of the nonspecific opiate receptor blocker, naloxone. Moreover, after receptive fields were enlarged by an episode of peripheral nerve stimulation, naloxone administration resulted in a shrinking of receptive fields.

Parallel human perceptual changes. Electroacupuncture has long been described as generating analgesia and other effects in humans that apply to body locations distant to the site of nerve trunk stimulation. Local and distant analgesic effects have been demonstrated objectively in several animal models.[9,80] Electroacupuncture in humans results in widespread increases of two-point thresholds that persist well after treatment.[90] Naloxone administration results in significant decreases in two-point thresholds.[83] Electroacupuncture- and naloxone-induced changes of tactile spatial acuity have magnitudes, distances, and time scales that are consistent with those of the receptive-field size changes induced by roughly cor-

9

responding procedures in cortical area 3b in our animal models.

Implantation of Always-innervated Island Pedicle Flaps

Cortical representational changes. Two neurovascular island pedicle-flap hand skin transfers have been investigated. In one experimental series,[52,53,55] a neurovascular island was transferred from the ulnar aspect of D4 to the ulnar aspect of the thumb. In a second series,[43] a neurovascular island was moved from the ulnar aspect of D4 to the radial aspect of D3. In both cases, the defect on ulnar D4 was repaired by a skin graft from the digit receiving the neurovascular island.

The cortical representation of the surfaces of the hand reorganized in both series, to encorporate the representation of the innervated skin island into the cortical map zone representing the *recipient* digit. In the D4 to D3 transfer (Fig. 8), a representation of the transferred island was retained in the zone of representation of the donor digit, but a second equally large, novel representation also emerged in the territory of representation of the recipient digit. In both regions, receptive fields from the island commonly extended across the midline of the recipient digit, combining novel skin inputs that would never normally occur.

In the D4 to D1 transfer (Fig. 9), somewhat to our surprise, the representation of the skin from ulnar D4 virtually disappeared from its anatomically appropriate representational zone, and within three months after the transfer had emerged in entirety in the cortical zone of representation of the thumb. There, many receptive fields, always appropriately aligned, extended from the island onto the adjacent radial thumb.

As with changes following (1) digital syndactyly, (2) reorganization after peripheral nerve regeneration, and (3) the synchronous stimulation of adjacent digits in a behavioral task, the marked representational changes following skin island transfers must necessarily be accounted for by the new *temporal* structure of inputs from the skin, as that is the only basis for skin inputs to signal the new locations of these innervated skin islands on the hand.

Parallel human perceptual changes. In some humans, stimulation of neurovascular skin islands can, in time, be correctly referred to the recipient digit.[61,82] In other transfers, subjects persistently refer the stimulation of the island skin to the donor site. Our studies indicate that the former might be expected to occur when the neurovascular skin island is inserted into a location with always-innervated neighboring skin, because input from the surrounding skin temporally coupled with input from the island is what must drive the representational translocation. If nearby neighboring skin is denervated, there is little basis for accomplishing a representational translocation.

We speculate that the more dramatic changes occurring after a long-distance transfer may reflect the relatively stronger influences of the cortical representation of newly surrounding skin when the island is farther removed across the cortext from its original location—and, hence, away from its original, powerful cortical network influences.[1,44]

Behavioral Training and Locationally Invariant Stimuli

Cortical representational changes. What happens to the skin surface representation if a stimulus is brought down onto an absolutely unchanging skin spot repeatedly, in a monkey trained to make distinctions about the temporal patterns of applied stimulation? Changes in the cortical representation of the hand induced by such inputs are startling[70,73,74] (Fig. 10 A). First, a large cortical area representing that skin spot emerges, across which all cortical receptive fields are virtually identical.

Second, those receptive fields and other receptive fields all across the zone of representation of that finger are several times larger than normal. Indeed, even though the stimulus has been spot-like and of such a low amplitude that it cannot directly excite surrounding skin of the hand, cortical receptive fields are also enlarged all across the zones of representation of *adjacent* fingers.

Note that in this special case, (1) the cortical

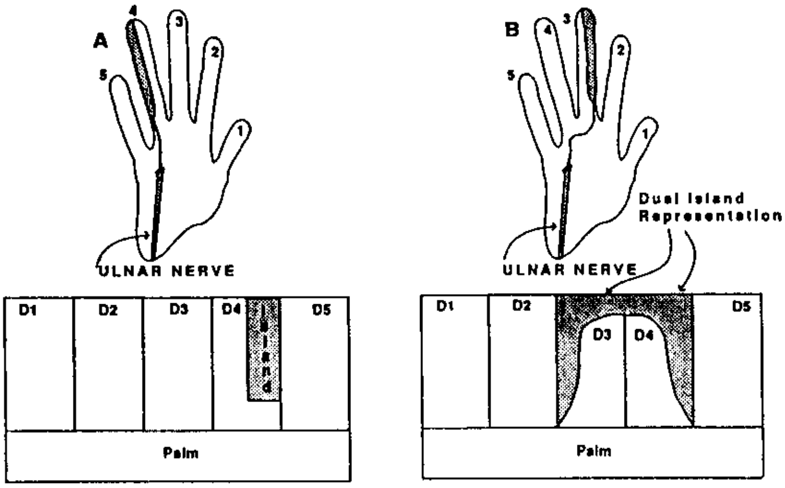


FIGURE 8. Remodeling of the area 3b representation of the hand (A) after an innervated skin island is transferred from the ulnar aspect of digit 4 to the radial aspect of digit 3 (B). Three or more months after such a transfer, two areas of representation of this former-digit-4 island skin were recorded: (1) one in the anatomically appropriate donor digit (D4) zone, and (2) a novel, emergent representation in the recipient digit (D3) zone (B). In both regions, many receptive fields were recorded that crossed from the skin island on digit 3 over the scar line to include skin on the always-innervated ulnar half of digit 3. Based on results from Merzenich et al.[43,53]

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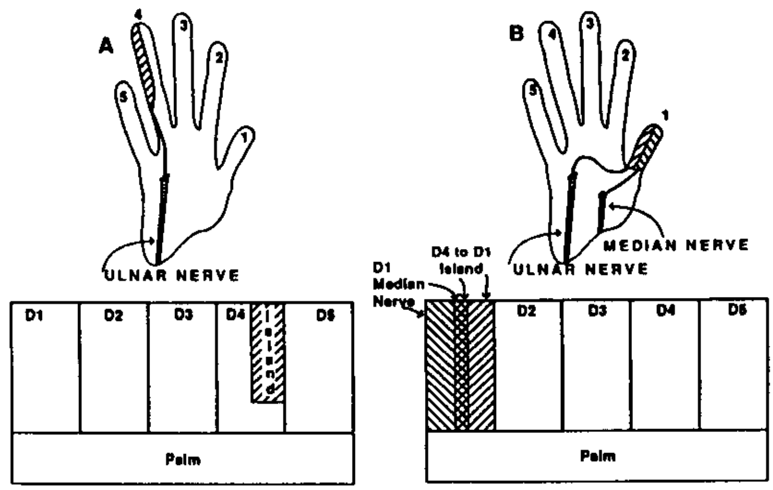

*FIGURE 9. Remodeling of the area 3b representation of the hand after an innervated skin island was transferred from the ulnar aspect of digit 4 to the radial aspect of the thumb. Three or more months later, the representation of the island skin, which was formerly in the fourth digit representational zone (**A**), largely disappeared in that cortical sector and emerged in entirety in topographic relationship to the representation of the surfaces of the thumb (**B**). In the thumb zone, many receptive fields extended across the scar line, i.e., incorporated novel combinations of inputs that would formerly have been represented several millimeters apart from one another in this cortical field. Based on results from Merzenich et al.*[44,52]

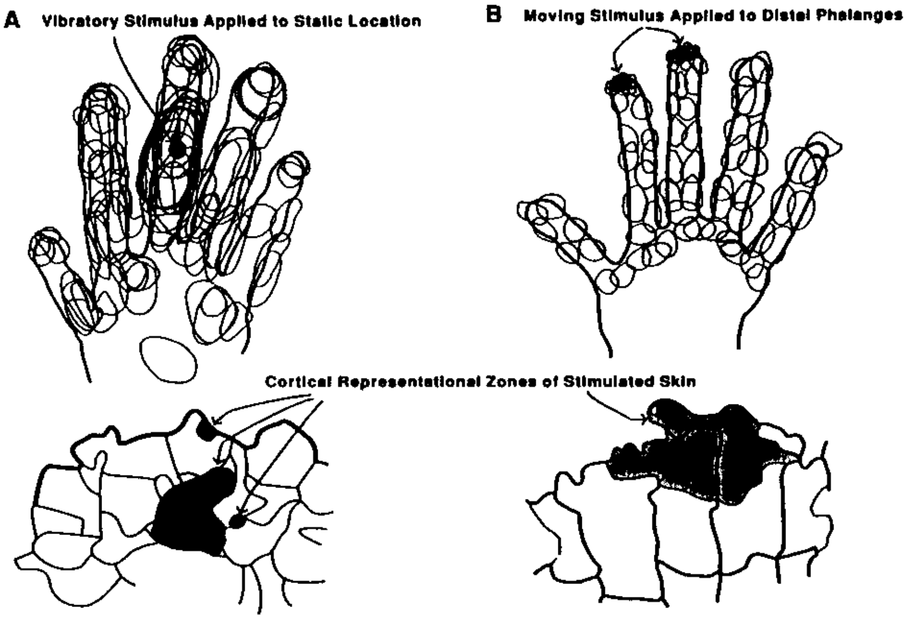

*FIGURE 10. Strikingly different representational changes evoked by attended behaviors in which tactile stimuli are applied to a static, unchanging skin location (**A**), or with stimuli moving across limited surfaces (**B**). In both cases, the cortical zones of representations of behaviorally important skin stimulation engaged progressively larger area 3b zones with progressive skill acquisition (bottom panels). With static stimulation, receptive fields and topographic order were crude, with effects on receptive field sizes of training at an invariant skin spot also affecting the zones of representation of several adjacent digits. With moving stimulation, receptive fields were small and represented the stimulated skin surface in very fine spatial grain. Based on results from Recanzone et al.*[70,73,74] *and Jenkins et al.*[33]

territory of representation of a particular skin surface enlarged, while receptive fields also enlarged, and (2) receptive fields over a cortical zone several hundred microns across had virtually complete overlap. Both of these findings are in conflict with the shifted overlap vs cortical distance "rule."

Parallel human perceptual changes. It has earlier been pointed out that the representation of the skin by smaller receptive fields—in finer spatial grain—probably equates with gains in spatial acuity. This simple example serves to illustrate that spatial acuity, absolutely localization, and haptic abilities can be substantially *degraded* by certain forms of conditioning or training. Preliminary psychophysical experiments (Dr. James Craig, Indiana University, work in progress) have confirmed this conclusion.

Behavioral Training with Moving Stimuli

Cortical representational changes. Why do cortical fields enlarge when the skin is engaged by stimulation at an invariant skin location? If we assume that the specific inputs that cortical neurons respond to normally involve competitive processes, then in this special case there is a competitive winner in the cortex, i.e., the small skin spot that receives all the stimulation. From the point of view of the cortex, any thalamic input that includes this spot in its receptive field is a strong competitor, indistinguishable from all others that share this credential. Cortical neurons over a large cortical zone are driven to represent the amalgamated consequence (Fig. 10 B), a large receptive field centered at the stimulated skin spot. The inputs that effectively drive neurons in this strongly excited zone influence the inputs that are effective for driving neurons in a surrounding zone. These horizontal cortical network influences result in the generation of almost equally large receptive fields in the surrounding region, representing the rest of the point-stimulated digit and the glabrous surfaces of adjacent fingers.

This skin stimulation situation is an exaggeration of what usually happens naturally, as stimuli would rarely be presented on such a heavy schedule to such precisely invariant skin loci. If these representational changes represent the consequences for a patch of cortex of creating a competitive winner, then what happens in the more common case in which stimuli in a heavily practiced behavior are presented at inconstant skin locations? That can be achieved, for example, by training a monkey to make distinctions about stimuli that *move* across the skin[33] (Fig. 10 A). In such monkeys, again the cortical territory of representation of the differentially stimulated skin surfaces enlarges, but in other respects, cortical remodeling differs. In these monkeys, receptive fields are extraordinarily *small*, and receptive fields shift continually across the expanded cortical representational zone.

Parallel human perceptual changes. Practice at a behavior in which stimuli are delivered at inconstant skin locations can result in a severalfold improvement of tactile acuity over that skin region, emerging over days of practice.[32,33,70] In general, practice at haptic skills generates substantial improvements in stimulus discrimination and recognition skills,[3,22,55] almost certainly attributable to practice-driven cortical representational change. In a wide variety of such experiments, effects of training are localized to the general region of the sensory epithelium engaged by training stimuli, but with some consequences of training conferred to a limited surrounding input zone.

DISCUSSION

How Do Altered Schedules of Activity from the Skin Contribute to These Examples of Cortical Representational Remodeling?

We have described ten peripheral manipulations, nine of which (recovery from peripheral nerve crush was the exception) led to significant cortical representational remodeling. Considering these manipulations together, what features of altered schedules of activity from the skin contributed to central representational change?

Cortical representations are time-based constructs. Taken collectively, these studies strongly support the conclusion that cortical representations are time-coincidence-based constructs. Important features of cortical representational changes (1) that result from nerve regeneration that shuffles skin-to-central nervous system addresses, (2) that follow the creation of syndactylized digits, (3) that result from moving innervated skin patches to new hand locations, and (4) that are the consequence of stimulation in behaving monkeys with static or moving stimuli *must* be explained by an input coincidence-based point-by-point reselection of afferent skin sources. By a time-coincidence-based integrative process, (1) skin inputs that respond together with high probability come to be represented together in cortical maps and (2) cortical maps represent temporal input continua, with sources of activities evoked from the skin nearly simultaneously in time overlapping in their representations with one another.

It should be noted that this basic view of the construction of cortical representations was first posited by the classical theorist Donald Hebb[29] and is a direct consequence of central mechanisms of synaptic plasticity by which the synaptic effectivenesses of inputs that nearly simultaneously engage central neurons are simultaneously strengthened. There is increasingly compelling evidence for the operation of such time-based "associative" input strengthening mechanisms in the cerebral cortex.[54,71]

Cortical reorganization following peripheral nerve injury or peripheral skin translocation involves a combinative consequence of changes in skin input origins, and experience-generated plasticity. After nerve regeneration, neurons in the dorsal root ganglion and at every higher level obtain new representational neighbors, consequent from input-address shuffling resulting from the regeneration process. After digital syndactylies or after skin island transfers, while skin-to-central nervous system addresses are largely unperturbed, the fused or transferred skin now has new skin neighbors, producing radically altered temporal structures of inputs evoked from the skin by natural stimuli. Representational changes that result from these afferent input manipulations arise in large part because of these profound changes in the spatial and temporal structures of inputs, and in large part by the normal operation of use-dependent cortical representational plasticity that accounts for our lifelong capacities to refine skin use with practice.

Processes of cortical reorganization are competitive. These studies also support the conclusion that many aspects of observed changes are explained by dynamic *competitive* processes in the central somatosensory system. Thus, for example, with the loss of inputs from a skin field or from an amputated finger or hand or arm, the representation of the intact surrounding skin expands competitively to occupy the cortical zones representing the silenced—now not effectively competitive—nerve(s). When the occupation of this cortical zone is completed, occupying inputs generate sharp boundaries indicating that they competitively divide the "new" territory that they now dominate. In the event of full recovery of the original inputs, e.g., following regeneration after a crush injury or with removal of an adapting tactile stimulus in the important experiments of Craig,[12] restored normal inputs gradually re-establish dominance over their approximately original territories. On the other hand, the temporally diffused inputs from a regenerated nerve are less effectively competitive, and as a result, it does not re-establish dominance over all of its original cortical representational territory.

The competitive nature of cortical representational remodeling processes is also indicated by behavioral experiments in which stimuli are applied to invariant or to inconstant skin locations. In the former case, powerful summative effects are attributable to a competitive winner, the invariant spot of skin that was strongly differentially stimulated. Completely different results occur when behaviorally important stimuli are presented to inconstant skin loci. In that case, every small skin locus provides effectively competitive inputs. As a consequence of this radically different competitive condition, smaller than normal receptive fields are generated, as the cortical

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network creates an abnormally fine-grained, spatially devolved representation of the engaged skin surface.

As with the coincidence-based Hebbian processes of integration that underlie many of these representational changes, there is a long history of studies of the distributed excitatory and inhibitory processes that underlie competition in cortical networks.

Horizontal spreads of effects via intrinsic cortical network connections contribute to these representational and perceptual phenomena. Engagement of any small part of cortical representations generates influences that spread well away from the core zone of cortical activation. If a human subject is trained in a tactile discrimination task, improvements in stimulus discriminability are recorded not just for the trained skin, but for a significant surrounding skin area. The same phenomena apply to cortical representational remodeling. When training is directed to a limited sector of skin, major changes are conferred on the cortical representation of the surrounding skin, well away from the core sector, presumably largely under the direct influence of this core zone at which maximum change is being generated.[54,70,73,74]

The domain of horizontal cortical network influences is also hypothetically revealed by the creation of multiple, widely separated receptive fields in the cortex following peripheral nerve regeneration after nerve section and reconnection.

Again, there are many precedents for these observations in studies of the neocortex, and they are now the subject of intense study.[54]

Other Factors Influencing Representational Remodeling

Modulation of cortical plasticity as a function of behavioral state. A growing number of studies of cortical plasticity in trained animals reveal that the remodeling of cortical representations by use is modulated as a function of behavioral state, and as a function of the strengths of reward or punishment in behavioral training. Thus, for example, representational changes evoked by behavioral training in somatosensory or auditory cortical fields such as those illustrated in Figure 10 do not occur when animals are stimulated on equivalently heavy stimulus schedules, but with that stimulation unattended.[33,73,74] Indeed, there is growing evidence that nonassociated "meaningless" inputs can actually drive negative representational changes in cortical representations.

Our own behavioral training experiments have been conducted with the use of operant conditioning paradigms employing positive (food, juice, water) reinforcing stimuli. In this behavioral context, representational changes progress gradually over a relatively slow daily improvement schedule. However, it is a well-established fact of experimental psychology that the rates at which behavioral changes are generated are a function of the strengths of cognitive drive or behavioral reinforcement. The great range in the power of cognitive drive provides a potential basis for generating much more powerful representational changes over much shorter rehabilitative training periods.

Pain. Under different circumstances, representational changes are either forestalled or dramatically accelerated by concurrent pain. Thus, for example, limb telescoping probably occurs in all patients without severe phantom limb pain.[30,36] In subjects with pain, the magnitude of body image changes—and inferred cortical representational change—is inversely related to pain magnitude. Indeed, when phantom limb pain is episodic, the phantom limb can appear to perceptually elongate during pain episodes, and shorten again in pain-free periods.

The influences of innocuous skin inputs in the antinociception system is a complex subject beyond the scope of this review. One possible example of such a link indicated by these cortical plasticity experiments comes from studies of the consequences of large-fiber afferent stimulation in peripheral cutaneous nerves. Changes evoked by that manipulation parallel described antinociceptive changes documented in animal and human models. For example, changes emerged all across the representation of the skin on that side of the body, and were completely blocked by administration of the nonspecific opiate receptor antagonist naloxone. While such studies are in their infancy, in extension they should add to our understanding of the bases of the antinociceptive effects of transcutaneous electrical nerve stimulation (TENS) and electroacupuncture.

In other settings, pain is a powerful behavioral reinforcer, and can very strongly facilitate representational change.

Other possible factors. Recent experiments conducted by Calford and Tweedale[7] suggest that innocuous C-fiber inputs from the skin may also contribute to cortical plasticity changes. Their studies indicate that there is a normal heavy afferent bombardment from non-nociceptive C-fibers that enables the maintenance of normal, small-sized cutaneous receptive fields in primary somatosensory cortex. If this C-fiber input is blocked by the administration of capsaicin to a nerve trunk, receptive fields immediately enlarge, on a scale resembling the changes recorded following peripheral nerve transection. There is probably a relationship between these effects and the consequences of large-fiber stimulation of peripheral cutaneous nerves, but studies designed to determine that relationship have yet to be undertaken.

Where in These Systems Does Remodeling Actually Occur?

A detailed consideration of the contributions of changes at different system levels to representational remodeling recorded in cortical area 3b following hand use or hand injury is beyond the scope of this review. Suffice it to say that: (1) Dramatic remodeling can occur at the level of the dorsal column nuclei following peripheral nerve transection or amputation.[41] (2) Dramatic remodeling can occur at the level of the thalamus following induction of lesions into the large fiber tract (the medial lemniscus) projecting to it from the dorsal column nuclei.[20,86] (3) Similarly, manipulations at the cortical level alone can induce representational plasticity.[64,72]

Taken together, these observations indicate that plastic changes following skin deafferentation or amputation are contributed to by changes at *all* somatosensory system levels, and that *all system levels have some capacity to undergo representational remodeling,* on their own.

At the same time, representational changes following peripheral nerve repair, skin island transfers, and behavioral training appear to arise primarily within the cortex itself. After nerve transection and reconnection, small receptive fields emerge at the thalamic level, but orderly representational topographies do not appear to be established at that level, while they emerge in the cortex.[23] After skin island transfers, thalamic representations are not remodeled, and no receptive fields combining inputs from the skin island and the recipient digit skin are seen. Such fields are common at the cortical level, in representations of the skin islands novel to the cortex, located in the zones of representation of recipient digits.[43,44] After behavioral training, ventrobasal thalamic representational changes only weakly reflect the much greater magnitudes of cortical changes (Wang X, Jenkins WM, Xerri C, and Merzenich MM, unpublished observations, 1992).[15]

In these other cortical plasticity models, then, some subcortical remodeling can occur, but it operates only on a limited spatial scale. Most of the changes described at the cortical level appear to arise there. This is not surprising, given the much more extensive anatomic spread of connections at the cortical level than in the ventrobasal thalamus or dorsal column nuclei.[34,53]

Finally, while it is beyond the limits of our purview, it should be noted that equivalently large-scale representational remodeling occurs in the spinal cord, and in motor systems.

Some Implications of These Findings for Sensory Rehabilitation

The nature of distorted sensations and the capacity for sensory rehabilitation in a patient with a specific hand injury reflect: (1) anatomic changes in input sources created by the injury; (2) differences in the temporal structures of afferent activity evoked from the altered hand; and (3) representational changes driven by hand use up to the time of examination. In organizing a rehabilitative re-education schedule, the principles governing cortical plasticity should be considered. To summarize:

(1) *Cortical representations are coincidence-based.* Any basis for perceptual confusion can be strengthened by simultaneously stimulating confused input sources. Separating confused representations probably requires heavy schedules of stimulation with spatially discrete inputs.

(2) *Cortical representations are competition-based.* Equal stimulations of normal skin and more weakly organized abnormal skin will always favor the former in the cortex over the latter. In principle, rehabilitative training should differentially engage the dysfunctional skin zone.

(3) *Cortical changes are modulated as a function of behavioral state and as a function of the strength of behavioral reinforcement.* Passive, unattended, or little-attended exercises are of limited value for driving central representational change. The more important the training exercise, the more powerful its consequences. The more feedback a subject gets relevant to correct response performance, the faster useful representational changes can be driven. *Skin use in a practice setting in which the patient is continually well-rewarded for correct performance trials ought to generate the most rapid representational changes.* The cognitive weights of correct response reward are an important consideration. Rewarding of errant responses can frustrate corrective representational remodeling.

(4) *Different stimulus inputs patterns can have very different cortical representational consequences, all of which are not necessarily positive.* Thus, for example, improvements in spatial and temporal acuity can be achieved independently by practice; a training regimen can result in improvements in temporal discrimination abilities while negatively changing tactile spatial acuity, and vice versa. That might explain how significant improvements in tactile recognition skills can be obtained in subjects that have no measurable gain in absolute localization, skin sensitivity, or spatial discrimination measures. In fact, *training should be designed to improve* ***both*** *spatial and temporal acuity.*

In trying to define ideal training strategies, hand rehabilitation specialists might consider the above principles in adopting specific alternative sensory re-education paradigms. It would appear highly likely that a training appliance/strategy could be developed that could very much accelerate and could significantly improve the quality of sensory recovery in nerve injury patients.

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