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Cortical Representational Plasticity

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Abstract. Recent experiments have shown that the effectiveness of the coupled excitatory inputs and intrinsic inhibitory processes controlling the overt excitatory responses of cortical neurons are dynamically alterable throughout life. Many neocortical functional plasticity studies demonstrating this alterability have been conducted in the somatosensory cortex. In this review, we briefly describe some aspects of the results of these studies. Features of the underlying processes of excitatory "input restriction" or "input selection" revealed by them are described. Some implications of these adaptive cortical processes for the origins of behavior are discussed.

CORTICAL REPRESENTATIONAL PLASTICITY

The alterability of overtly effective excitatory inputs of cortical neurons has been demonstrated in many experiments. Most have been conducted within the somatosensory system. Relevant findings include:

1) *Cortical representations are substantially reorganized after peripheral nerve transection or dorsal root section in adult rats* (Wall 1984), *cats* (Franck 1980; Kalaska and Pomeranz 1979), *and monkeys* (Merzenich et al. 1983a, b). Neurons everywhere across a broad cortical region including both the former zone of representation of the transected nerve and an extensive surrounding cortical zone acquire new effective driving inputs following such peripheral deprivation. Expansions of representations of surrounding skin surfaces into the deprived cortical zone are progressive (Merzenich et al. 1983a; Wall 1984), and the occupation of silenced cortical sectors begins to emerge almost immediately. With transection of a single peripheral cutaneous nerve, reanimation of the cortical zone whose effective excitatory inputs have been silenced is usually complete within a few days. However, further relatively

substantial alterations in effective driving inputs are recorded in monkeys over a subsequent several-week period (Merzenich et al. 1983a).

2) *Following digital amputation in raccoons* (Kelahan and Doetsch 1984; Rasmusson 1982) *and monkeys* (Merzenich, Nelson et al. 1984), *representations of the surrounding digits and palm enlarge to occupy the former cortical zones of representation of the missing digit(s).* Digital amputation constitutes a special class of nerve-transection experiments. In raccoons, inputs from different digits are largely segregated anatomically at the level of the cortex (Rasmusson and Nance 1985), and deep and high-threshold inputs from adjacent digits occupy much of the cortical zone formerly representing the amputated digit (Kelahan and Doetsch 1984; Rasmusson 1982). In owl monkeys and cats, there is substantial anatomical overlap in the zone of representation of the digits (Snow et al. 1987; see below). In monkeys, cutaneous representations of digital and palmar surfaces surrounding the amputated member enlarge topographically to completely occupy its former cortical zone of representation. As in simple nerve transection experiments with representational expansion, some skin surfaces come to be represented after amputation exclusively within the former cortical territory of the now-missing digit (Merzenich, Nelson et al. 1984).

With amputation of one or two digits, neurons over a continuous region encompassing at least two-thirds of the hand representational zone acquired new overtly effective excitatory inputs. With amputation of two digits, reoccupation of the silenced cortical zone was always incomplete; translocations in the cortical sites of representation of given skin surfaces did not exceed a distant limit of about 600–700 microns (Merzenich, Nelson et al. 1984).

3) *Inputs effective for driving cortical neurons have been demonstrated to change over time in the absence of any special cutaneous stimulation.* We have recorded substantial shifts in receptive fields in monkeys recorded with floating microelectrodes over time. Such electrodes are believed to maintain sampling of neuronal populations at a nearly constant cortical location. Shifts corresponding to cortical representational translocations of many hundreds of microns have been recorded in such experiments.

4) *Cortical representations in monkeys are substantially remodelled by a tactile behavior in which a restricted skin surface is differentially heavily stimulated* (Jenkins et al. 1984; Jenkins and Merzenich 1987; Merzenich 1987; Fig. 1). In such experiments, the territories of area 3b representations of restricted, heavily stimulated skin surfaces enlarge to a great extent in adult owl monkeys. When hand surface representations defined before and after such training are compared in detail, neurons over virtually the entire hand representational zone are seen to acquire newly effective driving inputs.

In a related experiment, cortical representations of the vibrissal representational zone (the barrel field) in adult rats have been found to be substantially reorganized following vibrissa trimming, resulting in the heavy differential stimulation of a limited subset of vibrissae for no more than a few experimental days (Yun et al. 1987; see also Hand 1982).

5) *There is a substantial reorganization of the area 3b representation of the skin surface in the region surrounding a restricted cortical lesion in adult monkeys* (Jenkins and Merzenich 1987). Through that reorganization, skin surfaces formerly represented in the cortical zone of the lesion come to be represented in the cortex surrounding the lesion. Neurons over a broad surrounding region at least several millimeters across are driven by newly effective inputs after this class of experimental or natural disturbance. This dramatic topographic reorganization in the region surrounding an infarct likely constitutes a fundamental basis for recovery from brain injury (Jenkins and Merzenich 1987).

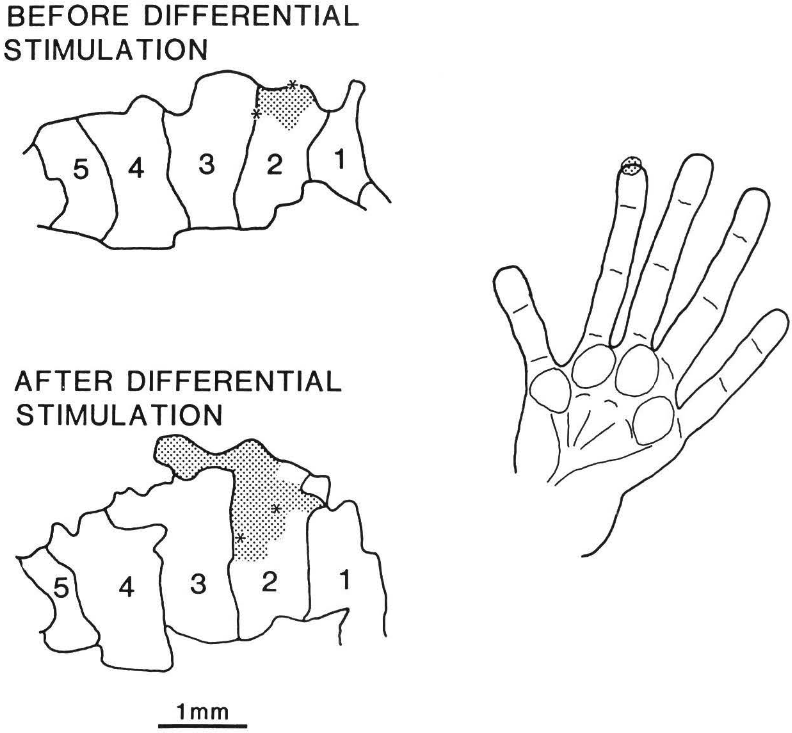
6) *The very large hand representational zone in the principal SII cortical field in adult macaques is completely occupied by inputs from other skin surfaces following ablation of the principal input sources of this cortical area, the SI cortical fields* (Pons 1987). "New" effective inputs principally represent the foot. In this functional reorganization, representational translocations of many millimeters in distance are recorded.

7) *The functional hand representational zone in an adult monkey is substantially remodeled after creation of a syndactyl condition* (Allard et al. 1985; Merzenich 1987). With two digits temporarily fused together following a surgical procedure minimizing the disturbance of peripheral innervation boundaries, the representational border normally recorded between two digits in the hand representation in area 3b is completely broken down (Fig. 2). Across sharp functional boundaries in the area 3b cortical representation of a normal adult monkey, receptive fields for neurons usually fall exclusively on one or the other of two adjacent digits. After creation of a syndactyl condition, neurons across a broad region between the zones of representation of the two fused digits respond to stimulation of them both.

8) *The hand representational zone in an adult monkey is dramatically reorganized after the transfer of an innervated skin island from one digit to another* (Clark et al. 1986; Merzenich 1987; Fig. 3). As in the syndactyl case, skin fields in these studies are cut along the lines of innervation of digital cutaneous nerves. Skin islands are transferred with their vasculature intact. They are traded with a second innervated skin island, or with a noninnervated graft from the digit receiving the innervated island.

From the point of view of central nervous system addresses, little has been altered peripherally by this manipulation, i.e., locations on the same skin are represented anatomically by unchanging populations in the digital cutaneous nerve and dorsal root ganglion.

After an island transfer the entire hand representation reorganizes, in large part to create a new topographic relationship between the island and the bordering skin on the recipient finger. Prior to this experimental



BEFORE DIFFERENTIAL STIMULATION

AFTER DIFFERENTIAL STIMULATION

Fig. 1—Outlines of the area 3b cortical territories representing the surfaces of the digits at two epochs in the life of a normal adult monkey. Maps were derived prior to initiation of a special behavior and about 3 months later, during which time this monkey had performed a task that involved differential, heavy stimulation of the tips of the distal phalanges of digits 2, 3, and occasionally 4 for about one hour/day. The differentially stimulated skin surface on digit 2 is indicated by stippling in the hand drawing at the right. Representational "maps" were drawn from definition of receptive fields defined within several hundred microelectrode penetrations into this area 3b zone at both experimental stages. Outlined territories are zones over which receptive fields were centered on digits 1 to 5. The zones of representation of the struck skin surface on the distal phalanx of digit 2 is stippled in both drawings, i.e., in this zone, all defined receptive fields overlapped onto this heavily stimulated surface. Note that after a period of differential digit tip stimulation in this and in five other monkeys studied with this paradigm, there was a substantial enlargement of its territory of representation. In this monkey, most of the gain in territory was from across the area 3b–3a border as defined functionally prior to the initiation of this digital stimulation behavior. On average, about half of accrued territory of representation in these monkeys is gained internally from within area 3b and about half from across the functionally defined rostral border of the koniocortical cutaneous hand surface representation. Redrawn from Jenkins and Merzenich (1987).

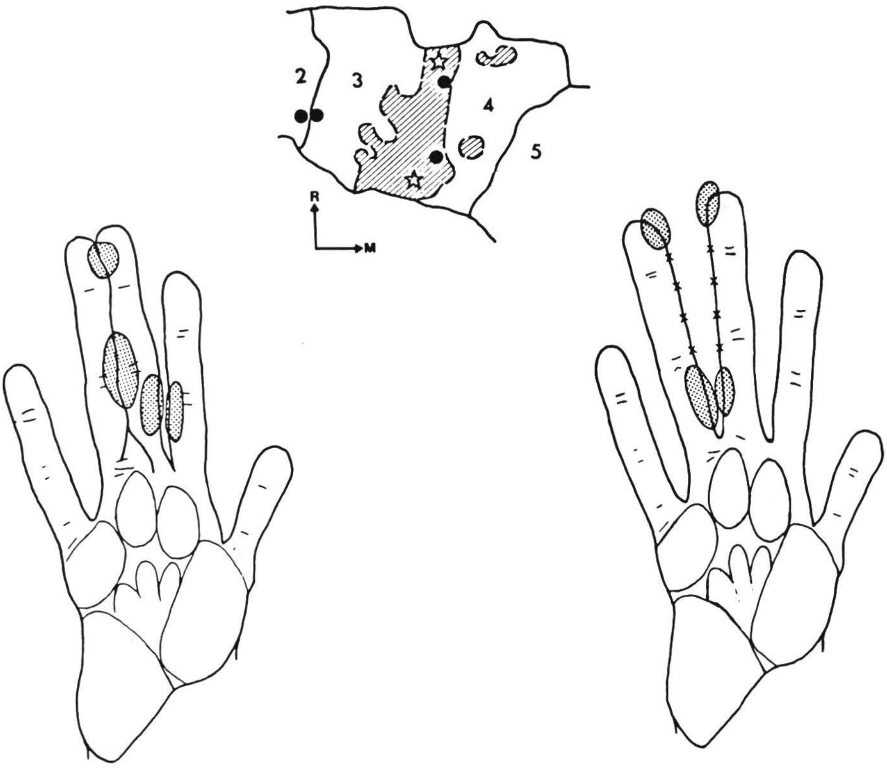


Fig. 2—Some features of the hand representation (center, top) in an adult owl monkey in which digits 3 and 4 were fused by a syndactyly surgical procedure for 7 months prior to the derivation of a highly detailed cortical map of this area 3b zone. In that map, all receptive fields defined within a large region (marked by diagonal striping) between the territories of the representations of the digits had receptive field components on both of them. Two such fields defined at the sites indicated by the black dots within this zone are illustrated on the syndactyl digits in the hand drawing at the left. By contrast, receptive fields defined for neurons across normal sharp digital representational "discontinuities" responded exclusively to stimulation of one or the other of the two adjacent digits as illustrated, for example by the two typical nearby penetrations across the digit 2–digit 3 border, also shown in the hand drawing at the left.

At the end of these experiments, the syndactyl digits were surgically separated, and receptive fields again defined within the zone of double-digit receptive fields. Two such fields, typical of nearly all acutely recorded within this zone (recorded at the locations marked by stars in the map) are shown in the hand drawing at the right. Both had receptive field components on the two adjacent digits, a response feature encountered infrequently in normal maps in area 3b in adult owl monkeys.

manipulation, these newly topographically related skin surfaces were represented at cortical locations hundreds of microns apart from each other. Again, in these preparations, new excitatory receptive fields emerge for neurons over most of the hand surface representation in cortical area 3b. Control experiments confirm that these effects are central in origin, i.e., they cannot be accounted for by peripheral nerve sprouting.

ASPECTS OF FUNDAMENTAL MECHANISMS UNDERLYING REPRESENTATIONAL PLASTICITY

Common features of representational reorganization reveal important general aspects of neural processes underlying this representational dynamism. *An*

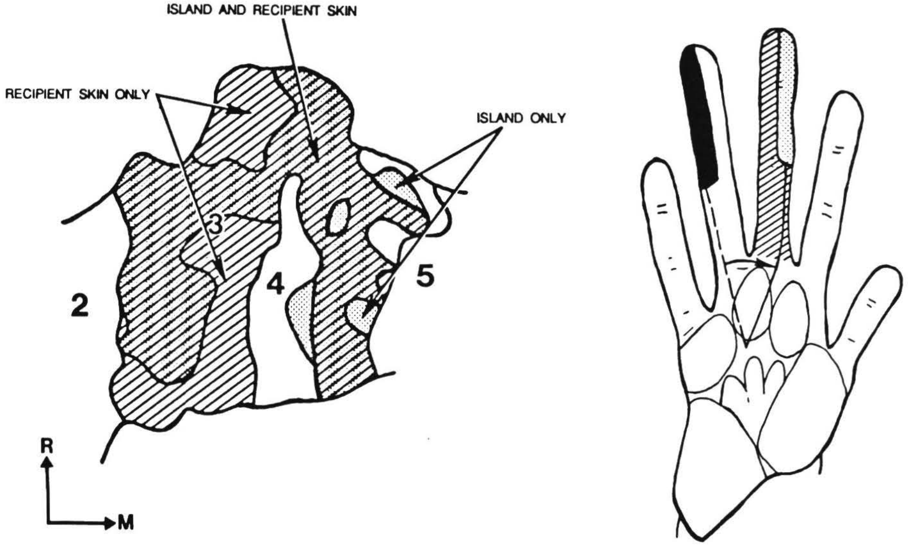


Fig. 3—Cortical representational map derived 6 months after transfer of an innervated, vascularized island pedicle from the ulnar aspect of digit 4 to the radial aspect of digit 3 in an adult owl monkey. A denervated graft derived from digit 3 was transferred back to close the defect on digit 4. A cortical map derived by definition of receptive fields within several hundred microelectrode penetrations is shown at the left. There, the skin on the recipient digit is marked by diagonal striping; the zones in which receptive fields exclusively represented the island are stippled. Note that over the largest demarcated zone, receptive fields are partly on the island skin and partly on the skin of the recipient finger. These skin surfaces are normally represented in cortical zones separated by more than 500 microns from each other in adult owl monkeys. Control experiments confirm that this dramatic representational reorganization is due to central and not peripheral effects; when the digital nerves innervating the island or ulnar recipient skin are anesthetized or cut, receptive field boundaries formerly representing the island skin invariably terminate along the scar line.

overlapping topography is commonly conserved, while cortical representations are reorganized. While there may be manifold enlargements or retractions in the extents of cortical territories representing given skin surfaces over time, a continuous, overlapping topographic representation of the skin surface is usually recorded at all reorganizational stages (Allard et al. 1985; Clark et al. 1986; Jenkins et al. 1984; Jenkins and Merzenich 1987; Merzenich 1987; Merzenich, Jenkins et al. 1984; Rasmusson 1982). Analysis of the results of these many experiments reveal that neurons at any given area 3b location can represent any given skin surface located over a relatively large peripheral extent at different times in the life of an adult monkey. For example, neurons normally representing a small skin surface location of the hand (e.g., usually a fraction of the surface of a digital phalanx) have the capacity for representing any skin surface region over at least one-third of the hand, and possibly a significant sector of the face or wrist. Thus, there are hundreds to thousands of possible receptive fields for neurons at a given cortical location at different times in the life of an adult monkey. Nonetheless, topographic order in the representation of skin surfaces is the rule.

Representational plasticity is probably accounted for by alterations in the functional effectivenesses of always present, divergent afferent inputs (Merzenich 1987; Merzenich, Jenkins et al. 1984; Merzenich et al. 1983a; Merzenich, Nelson et al. 1984). A number of studies have revealed that the "anatomical map" of excitatory thalamic afferents representing a restricted skin surface is crude and broadly overlapping compared with the "functional map" of overtly effective excitatory inputs recorded at any moment in the life of an adult monkey or carnivore. For example:

1) The convergence of excitatory inputs from relatively extensive skin areas to specific cortical area 3b loci has been revealed by the injection of the GABA receptor blocker bicuculine (Dykes et al. 1984; Hicks and Dykes 1983). Bicuculine injections in the somatosensory cortex in the cat result, on the average, in an approximately eight-fold enlargement of hindpaw cortical receptive fields; enlargement is apparently limited to neurons with quickly adapting response characteristics. Greatly enlarged receptive fields are excited relatively uniformly, i.e., emergent excitatory inputs are indistinguishable in their driving effectiveness from those manifested in preexperimental receptive field inputs.

2) Receptive fields are also enlarged by the electrical stimulation of a peripheral cutaneous nerve (Recanzone et al. 1986; Recanzone et al., submitted; Fig. 4; see below). Excitatory receptive field enlargements recorded after minutes to hours of peripheral nerve stimulation are recorded throughout area 3b, i.e., presumably occur for neurons in locations at which responses are both slowly adapting and quickly adapting. Again, these often greatly enlarged receptive fields are relatively uniformly excited. Possible mechanisms of origins of this nerve stimulation-induced change in input

selection are discussed below. Again, these studies manifest an extended, powerful, and immediately accessible repertoire of potentially effective excitatory inputs.

3) Neuronal receptive fields defined with cutaneous electrical stimulation are larger than receptive fields defined with natural stimuli. On the average, differences parallel those recorded before and after bicuculine injections in the cortex, or after a several-hour episode of peripheral nerve stimulation. In a variation of this observation, the cortical zone of projection of any peripheral cutaneous nerve defined by electrical stimulation is far larger than the cortical zone over which the skin surface represented by the nerve is manifested by natural stimuli (see Towe et al. 1964).

4) The cortical territory intensely marked by 2-deoxyglucose label after restricted natural cutaneous stimulation is commonly substantially larger than the territory over which neurons are overtly driven by such stimulation (Juliano and Whitsel 1985). The spreads of inputs indicated by such studies are also greater than those that might be anticipated from the 3–10X receptive field enlargements recorded after bicuculine administration, or after continuous peripheral nerve stimulation. Labelling across these extended regions can be surprisingly uniform.

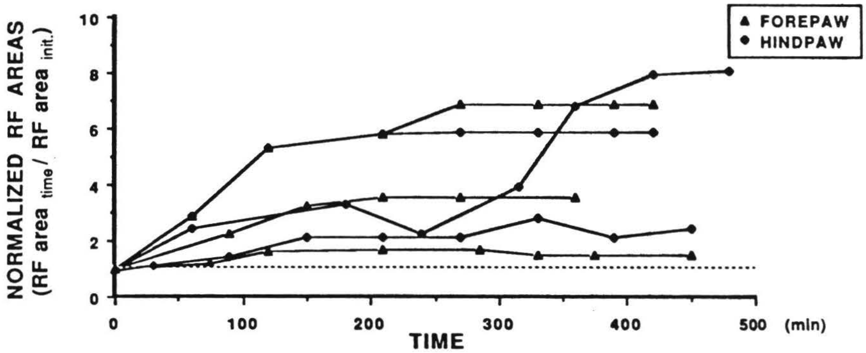


Fig. 4—Receptive field sizes of neurons defined at eight cortical loci within the forelimb and hindlimb representational zones in area 3b in an adult cat, plotted as a function of the duration of 20 pps electrical stimulation of the ulnar nerve in the distal foreleg. On average, roughly five-fold increases in the extents of receptive fields are induced throughout the contralateral body surface representation by such stimulation. Note that in the hindlimb representational zone, there is no directly evoked neural response to electrical stimulation of this forelimb nerve. A series of controls demonstrate that such receptive field size changes are a direct consequence of electrical stimulation of the peripheral nerve (Recanzone et al. 1986, 1987).

Such studies indicate that the anatomical map of the skin surface is far cruder than the functional map of overtly effective excitatory inputs defined by the use of simple, natural stimuli at any given moment in the life of the adult primate or carnivore.

5) Inputs from far broader sources than those that overtly drive cortical neurons *commonly* evoke excitatory postsynaptic potentials within them (Zarzecki et al. 1983; Zarzecki and Wiggin 1982). Such functionally demonstrable excitatory inputs are recordable by stimulation of different nearby peripheral nerves on distance scales indicating a spread of excitatory inputs representing given peripheral skin locations in the somatosensory cortical fields of carnivores of up to at least several millimeters.

6) Individually labelled ventroposterior cell afferent arbors spread relatively widely within the middle cortical layers in even the koniocortical field, area 3b, of monkeys and carnivores (Garraghty and Sur 1987; Landry and Deschenes 1981). Physiological mapping of the arbors of single ventroposterior thalamic units, representing specific skin loci referenced to the cortical zone of overt representation of that skin locus, reveal a mismatch (Snow et al., submitted; e.g., Fig. 5). Both electrophysiological arbor-mapping experiments and single fiber labelling studies in New World monkeys indicate that individual arbors may spread up to more than 2 mm across the horizontal dimension in the koniocortical somatosensory representation, area 3b.

Electrophysiological mapping studies also suggest that arbors from across the isorepresentational axis of the ventroposterior thalamus (see Jones et al. 1982; Kaas et al. 1984) project with substantial divergence into cortical fields (Snow et al., submitted). This dispersion of anatomical inputs representing common peripheral skin locations — along with the relatively broad distribution of individual afferent fibers — underlies the generation of the relatively crude ("degenerate"; see Edelman 1978) "anatomical maps" in this system.

The limits of anatomical divergences of projections presumably account for observed distance limits for representational reorganization (Merzenich 1987; Merzenich, Jenkins et al. 1984; Merzenich, Nelson et al. 1984). That is, the site of representation of a given skin surface can shift within the neocortex to only a limited extent (see Fig. 6). Representational changes up to about 1.5–2 mm have been recorded in cortical area 3b, but shifts are usually not greater than about a thousand microns. Greater changes have been recorded in the more divergently connected cortical area 1 (unpublished observations), and substantially greater representational translocations have been recorded in the principal SII field in macaques (Pons 1987).

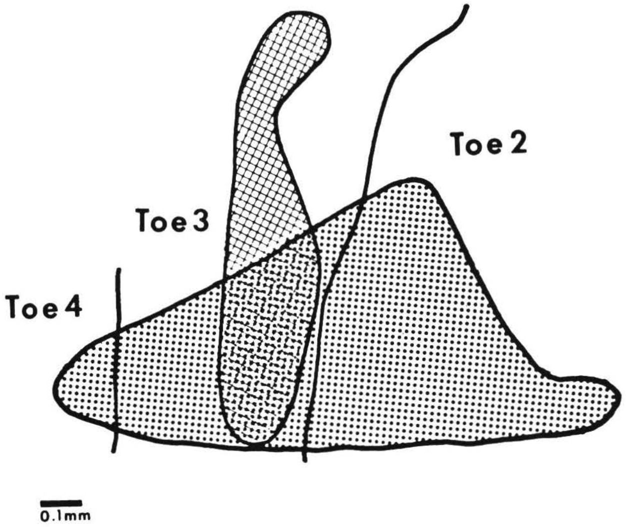


Fig. 5—Surface view of the territory of distribution of the cortical arbor of a single ventroposterior nucleus neuron representing a restricted cutaneous receptive field on the surface of digit 3 in an adult cat (dotted). The arbor boundaries were defined to within a few tens of microns by low-amplitude antidromic microstimulation of this neuron in multiple cortical penetrations (dotted). The territory over which cortical multiunit receptive fields overlapped with this single thalamic neuron's receptive field is indicated by the cross-hatching. This order of mismatch between the distributions of arbors and the cortical zone of representation of the skin surface represented by studied thalamic neurons (in this case, the arbor extended into the zones of representation of both adjacent digits) was common. Redrawn from Snow et al. (1988).

With changes in representational magnification, there are corresponding inverse changes in receptive field size (Jenkins et al. 1984; Jenkins and Merzenich 1987; Merzenich 1987; Merzenich, Jenkins et al. 1984; Merzenich et al. 1983a; Merzenich, Nelson et al. 1984). That is, when representations expand or contract, the represented skin surface is commonly represented in finer or coarser representational grain, respectively. This accounts for the general rough maintenance of a percentage overlap versus cortical distance rule described for somatosensory cortical fields 3b and 1 in normal adult monkeys (Sur et al. 1980; see also Merzenich et al. 1983a).

It should be noted that significant exceptions to this rule have been recorded. The most important, discussed later, is manifested by the creation, under special experimental conditions, of large regions in the neocortex within which all neurons have very similar receptive fields.

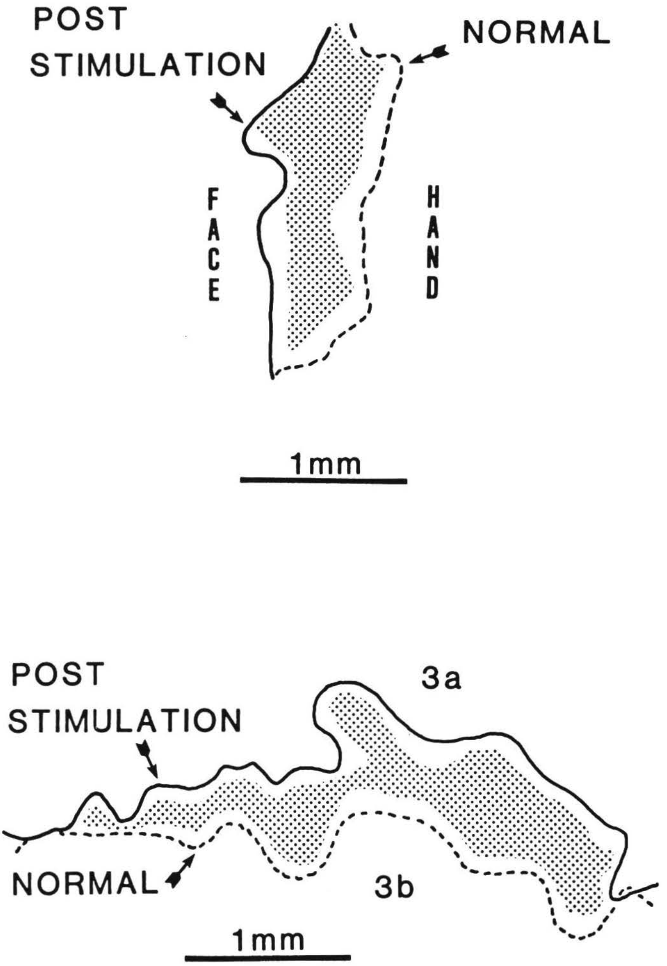


Fig. 6—Differences in the locations of the hand-face (upper) and area 3b-area 3a borders (lower) defined in an adult owl monkey before and after a period of intense behavioral training (see legend, Fig. 1). The stippled zones mark the minimal territories over which receptive fields for neurons at those locations were determined to have moved from the face to the hand, or from deep characteristically-area-3a responses to cutaneous characteristically-area-3b responses. In this zone, there is a direct overlap of microelectrode penetrations in which receptive fields were either (upper) on the face in the first map, and on the hand in the second; or (lower) deep responses predominantly from muscle and joint afferents in the first map, and low-threshold cutaneous responses in the second. Significant representational translocations are recorded along these borders in nearly every animal from which more than one representational map has been derived. Translocations never exceeded a distance limit of about one mm. See text for further details and some implications.

It must be emphasized that *dynamic "input restriction" or "input selection" applies to all of what have been termed the "static" features of responses of cortical neurons* (Mountcastle 1978). The receptive field is, of course, only one easily definable aspect of "selected" responses. "Representational reorganization" experiments should be interpreted as reflecting a process of restriction or selection of candidate afferent inputs; *any* of the available fundamental cortically projecting input combinations can, by use, presumably emerge effective for driving neurons at a given neocortical location. For example, the selection of slowly adapting or quickly adapting afferent populations constitutes a second apparent selected input category in the area 3b somatosensory representation in the owl monkey. In most monkeys, slowly adapting responses are recorded over only limited area 3b sectors. However, map reorganization studies indicate that these zones of SA representation can be subverted by QA responses, and *vice versa*. To cite one example, no SA responses have been recorded over greatly enlarged representations of the differentially stimulated surfaces in monkeys performing a behavioral task in which heavy episodes of 20/second vibratory stimulation were incurred. In another example, large sectors of the cortex of several monkeys presumably having abnormally heavy static hand stimulation (two of which were blind) had overwhelmingly predominant slowly adapting responses.

It is increasingly clear that *input coincidence can influence afferent input selection* (Allard et al. 1985; Clark et al. 1986; Edelman and Finkel 1985; Finkel et al. 1987; Merzenich 1987; Merzenich, Jenkins et al. 1984). Neocortical representations obviously do not strictly reflect the anatomical distributions of afferent excitatory inputs. Given the fact that neurons at any given cortical location can represent any of hundreds or thousands of specific receptive fields over a relatively large skin surface region at different times in the life of an adult mammal, what accounts for the afferent restriction or afferent selection underlying the generation of recorded receptive fields? What is the mechanistic basis of representational topography? A series of experiments indicates that, considered from the perspective of afferent inputs, cortical representations may "map" probabilities of coincident or nearly coincident inputs. Thus, for example:

1) Representational discontinuities between digits in monkeys are known to be functional (and not anatomical) constructs, since they *move* within the neocortex in most of the above-described owl monkey map-alteration experiments (e.g., see Merzenich, Nelson et al. 1984). We hypothesized that interdigital representational discontinuities normally arise because of the largely temporally independent stimulation of the skin of adjacent digits. *Digital syndactyly experiments* (Fig. 2) support that conclusion. After a period of digital fusion, the representational discontinuities between the

fused digits break down. That is, across a broad cortical zone encompassing the former regions of separate representations of the facing aspects of two adjacent digits, neurons develop receptive field components that extend onto both digits (Allard et al. 1985; Merzenich 1987). That arises, we believe, because fused surfaces are almost invariably excited coincidentally.

With acute surgical separation of digits after a long period of syndactyly, a study of neurons in this zone reveals that they almost invariably retain receptive field components on both digits — something normally infrequently recorded. Such controls demonstrate that the emergence of 2-digit receptive fields after syndactyly is not an artifact of peripheral regeneration, but rather an unequivocal consequence of a central change in selected excitatory inputs. The observed changes in overtly effective inputs and topographic representations are almost certainly temporally based.

2) Cortical representational reorganization recorded in the *island pedicle transfer experiments* (Clark et al. 1986; Merzenich 1987) also implicates temporal coincidence as playing a fundamental role in afferent input restriction or selection. There, a continuously innervated and vascularized island of skin is moved from its normal skin location to a new one. As noted above, the transfer is made under conditions that limit changes in skin-to-central nervous system addresses. In these preparations, the scar line initially constitutes a border for all receptive fields, and many fields have components on both the nontransferred part of the donor digit and on the transferred island. In time, these 2-digit receptive fields are less common, and very many fields are found extending across the scar line from the transferred island onto the surrounding recipient skin. Those skin surfaces are normally represented at cortical locations hundreds of microns apart.

Again, anesthetic or nerve transection controls at the end of these experiments demonstrate that these changes are in selected excitatory inputs; they are not accounted for by peripheral effects. They can only be accounted for by a coincidence-based selection of new combinations of effective inputs.

3) *Nerve transection-reconnection experiments* also manifest a role for input coincidence for the generation, maintenance, and alteration of cortical receptive fields and representations. With nerve transection and reconnection, there is a pseudorandomization of the peripheral field locations of regenerating afferent fibers (see Wall et al. 1985). Nonetheless, following transections of small peripheral cutaneous nerves, reestablished representations are usually in register with the representations of the surrounding skin. With regeneration of larger nerves, reorganizational topography is much more complex. Nonetheless, continuously shifting overlaps of receptive fields are reestablished with reorganization in adult monkeys studied after nerve regeneration (Merzenich 1987; Wall et al. 1985). The reestablishment of small receptive fields in these monkeys (in which randomization of central nervous system to peripheral skin

addresses should result in receptive fields covering most or all of the skin field of the transected nerve) must involve a temporally based input selection process. The reestablishment of map topography almost necessarily requires operation of a coincident-based selection process. By this interpretation, details of map topography reflect the probabilities of coincident or nearly coincident inputs. Adjacent skin surfaces are represented in adjacent locations in large part because there is a high probability that they will be excited nearly coincidentally.

4) *Studies of chronically coincidentally excited vibrissae* conducted in the barrel fields of adult rats are also consistent with these conclusions. If two vibrissae are coupled so that they are with high probability excited coincidentally, they are highly likely to costimulate cortical neurons over most of the cortical zone in which they are represented (Yun et al. 1987). Such studies have been conducted by an experimentalist who is blind to the vibrissae coupled over a 1 to 2 week period prior to derivation of the electrophysiological map. Before the map is derived, all vibrissae are trimmed to a constant length, and there is no indication of which vibrissae have been coupled. Rats are maintained in a rich tactile environment. Again, these studies demonstrate an apparent powerful influence of the temporal correlations of inputs for shaping selected cortical receptive fields.

Changes in input restriction or selection manifested in these cortical experiments are largely accounted for by changes occurring at the cortical level. The greatest anatomical dispersion of inputs in the lemniscal limb of the somatosensory system is in the thalamocortical projection. Even if there is substantial alteration in somatosensory representations at subcortical levels (which has been demonstrated to occur; see Millar et al. 1976; Wall and Devor 1978), given the great divergence and convergence of thalamocortical inputs representing any given skin surface there is a *requirement* for the operation of input-selection mechanisms at the cortical level.

Changes in representation across the representational borders of area 3b manifest purely cortically based input restriction (Fig. 6). Thus, for example, movements in the representation of the hand surfaces into the cortical zone of representation of the face — or vice versa— are common (Fig. 6, top). In the thalamus, there is a complete separation of anatomically distributed inputs representing the hand and face within the lateral and medial parts of the ventroposterior nucleus. Similarly, primary sources of inputs from muscle and joint afferents and cutaneous afferents dominating the responses of areas 3a and 3b, respectively, are segregated in representation in the thalamus. Nonetheless, the deep-cutaneous border between what are functionally defined as areas 3a and 3b is highly mutable (Fig. 6, bottom).

In both of these examples, substantial anatomical overlap of projections occurs over a reorganizing zone at the cortical but not at the thalamic level.

Representational reorganization recorded in these zones is like that recorded elsewhere within area 3b or area 1. *It must be accounted for by intrinsic cortical processes.*

Input selection or input restriction is by neuronal groups (Edelman 1978); *groups are dynamic, functional, not fixed anatomical units; and sizes of neuronal groups are manipulable.* Cortical mapping studies in the somatosensory sphere support the contention that input selection is by neuronal groups normally having significant (several tens of microns) horizontal extents. While technical problems limit the present proofs of the existence of discrete neuronal groups in area 3b, they have been unequivocally demonstrated in several special classes of experiments. First, following peripheral transection and regeneration of a large cutaneous nerve, neurons at given cortical loci have multiple receptive fields located at several different locations across the skin field of distribution of the nerve (Merzenich 1987; Paul et al. 1972; Wall et al. 1985). Specific unique combinations of receptive fields are recorded for *all* neurons that respond to tactile stimuli recorded in vertical penetrations across the depths of cortex, and for *all* neurons across a significant horizontal distance. These special mapping studies reveal discretely bounded cortical neuronal groups. Second, under a variety of experimental circumstances (one of which is described in a motor cortex study below), greatly enlarged neuronal groups have been generated. These "supergroups" often extend over hundreds of microns across the cortex. Within them, all member neurons have identical or nearly identical response characteristics. Among other circumstances, they have been recorded: (a) In several animals wearing chronic digital casts; (b) in several but not most adult cats studied after stimulation of peripheral cutaneous nerves; and (c) in two cats in which differential stimulation of small hair patches was facilitated over a several day period. In all of these instances, neurons over cortical sectors up to nearly 1.5 mm across had virtually identical receptive fields.

It is clear that the dimensions of input-selecting neuronal groups are dynamic. It is highly likely that they are generated, sustained, and compete for domination of neurons along their mutual borders under control of afferent input synchronization (Edelman and Finkel 1985; Finkel et al. 1987; Merzenich 1987).

Finally, *modulatory inputs control afferent input effectiveness.* We still have only very limited evidence in somatosensory studies that input effectiveness is modulated as a function of behavioral state. Better examples from the motor cortex and the auditory cortex will be described later.

At the same time, we have conducted a series of acute experiments that have generated new insights into possible behaviorally contingent sources of modulatory inputs. In those studies, as described above, we were able to produce large changes in cortical receptive fields by electrical stimulation of afferents in a single peripheral cutaneous nerve (the ulnar nerve) in sodium pentobarbital-anesthetized cats (Recanzone et al. 1986; Recanzone et al., submitted). Receptive fields at most or all locations in the contralateral body surface representation were enlarged substantially by such stimulation (Fig. 4). Fields could increase more than tenfold in extent at a given cortical location; the mean areas of poststimulation receptive fields were 4.8 times greater than prestimulation receptive fields defined at the same or nearly the same cortical locations. Substantial receptive field enlargement was recorded after about thirty minutes of peripheral nerve stimulation. Fields continued to enlarge for several hours, then usually stabilized in size. With stimulation of a forepaw nerve i.e., the ulnar nerve, receptive field size changes were as great or greater in the hindpaw representational zone in area 3b as in the forepaw zone. Forepaw nerve stimulation resulted in no evident evoked discharges within the hindpaw representational zone.

These widespread effects on cortical input selection or restriction indicate that stimulation of a peripheral cutaneous nerve drives a global modulatory system that modifies the effectivenesses of cortical inhibitory and/or excitatory inputs on a major scale.

Stimulation of a peripheral nerve at parameters paralleling those in this study have long been known to produce analgesia within the field of the stimulated nerve. Such stimulation administered *via* electroacupuncture or TENS stimulators constitutes a common treatment in humans with intractable pain. Recent animal experiments have demonstrated that large-fiber afferent stimulation-induced analgesia is not restricted to the spinal segment of the stimulated nerve; analgesia can be widespread (Chung et al. 1984; Gamble and Milne 1986; Toda and Ichioka 1978). This peripheral nerve stimulation-induced analgesia is reversed by the systemic injection of the opiate antagonist naloxone. Taken collectively, these studies strongly implicate an endogenous opiate "antinociception system" (Basbaum and Fields 1984) in the mediation of these analgesic effects.

As with analgesia, naloxone halts and usually reverses the cortical receptive field size changes recorded after peripheral nerve stimulation (Fig. 7). Receptive fields monitored throughout the stimulation period normally expanded during the first several hours of stimulation, then stabilized in size (Fig. 4). If naloxone was injected during the stimulation period, the receptive field size normally stabilized in size or, more commonly, retracted to approximately the original size, then recovered with time and resumed expansion (Fig. 7A). Continuous infusion of naloxone throughout the stimulation period resulted in a maintaining of the receptive field at a small size (Fig. 7B).

Thus, these results indicate that the modulation of cortically recorded receptive field sizes by electrical stimulation of a peripheral nerve involves an endogenous opiate system.

These findings are important from several perspectives. Manipulation of levels of endogenous opiates have been demonstrated to affect learning, memory and selective attention in humans (Arnsten et al. 1984; Gallagher et al. 1985; Izquierdo and Graudenz 1980; Messing et al. 1979; Squire and Davis 1981). There is also behavioral evidence in humans that the coupling of electrical stimulation of large fiber afferents (e.g., in electroacupuncture) with passive peripheral stimulation — or naloxone administration — can affect the time courses of recovery from stroke (Baskin et al. 1984; Hoang 1981). In general, these stimulus-induced reorganizational changes conceivably constitute a basis for some of the manifold (largely undocumented) "central effects" of electroacupuncture.

How are these modulatory effects related to those attributed to other forebrain modulatory systems? Another example studied is the established role of cholinergic and noradrenergic systems in visual cortex development. These inputs have been shown to enable the formation of ocular dominance columns in the kitten during development; by eliminating or reducing the concentrations of both acetylcholine and norepinephrine in the visual cortex, one can significantly decrease the degree to which ocular dominance columns are formed during the critical period (see Bear and Singer 1986; Singer 1987). Interestingly, electrical stimulation of a peripheral nerve or administration of opioid compounds have been shown to increase acetylcholine release in the cerebral cortex of adult rats (Jhamandas and Sutak 1976, 1980, 1983). Stimulation-induced increases are reversed by the administration of naloxone. Iontophoretic application of ACh into the primary somatosensory cortex in anesthetized cats increases the responsiveness to tactile stimulation, and coupling the application of ACh to either tactile stimulation or glutamate iontophoresis enhances the response further (Metherate et al. 1987). These findings are consistent with the hypothesis that tactile stimulation results in a release of endogenous opiates which triggers ACh release — thereby ultimately increasing input effectivenesses.

In humans, it has been argued that the behavioral effects of opiate-level manipulations are mediated by or facilitate acetylcholine- and norepinephrine-based modulatory mechanisms (e.g., Gallagher et al. 1985; Izquierdo and Graudenz 1980).

SOME PERCEPTUAL PARALLELS

There are a number of simple perceptual parallels to this observed representational plasticity in the somatosensory system. For example, there are severalfold changes in tactile acuity in monkeys and humans attributable to practice engaging restricted skin surfaces (see Jones et al. 1977; Gibson 1953). Such changes at least roughly parallel, in their time courses and magnitudes, the changes in the magnifications and grains of representation of skin surfaces recorded in experienced monkeys. Discrimination of textures and recognition of felt objects based upon spatial cues improves substantially with practice.

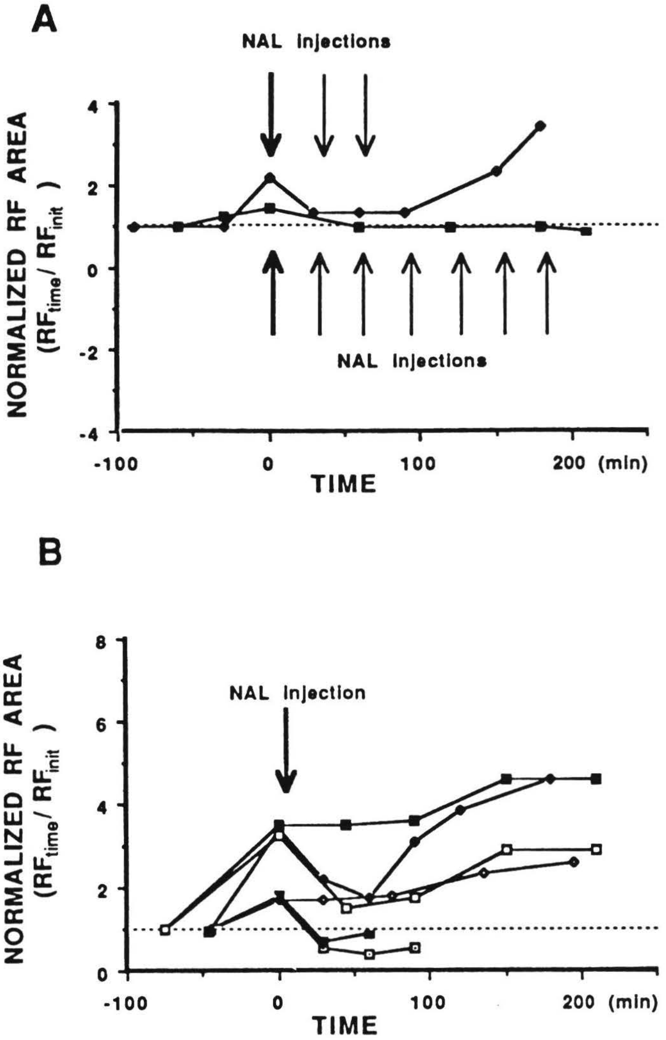


Fig. 7—Receptive field sizes change with continuous peripheral nerve stimulation and naloxone injections. Receptive field sizes throughout the contralateral body surface representation in area 3b of adult cats invariably enlarge over a several-hour period of peripheral nerve stimulation. If naloxone is introduced (at 0 on the abscissa) while a forelimb peripheral nerve is being continuously stimulated, initially enlarged receptive fields usually shrink to near their prestimulation sizes. If naloxone injections are repeated at half-hour intervals to maintain a high blood level, small receptive field sizes can be sustained (A). In a period well after a single naloxone injection (B), or after cessation of repeated injections (upper curve in A), receptive fields again enlarge, presumably as naloxone binding again declines.

Again, major effects are recorded over the time period in which the maximal changes in cortical representational detail would be expected. Spatial tactile acuity commonly improves significantly on the stump skin of amputees (Haber 1955; Teuber et al. 1949). Again, the time courses and extents of such changes in humans parallel those for observed reorganizational changes in cortical somatosensory representation following digital amputation in monkeys. Tactile acuity has been shown to be rapidly degraded following acupuncture (Wang et al. 1981); again, we have observed substantial increases in receptive field sizes occurring rapidly after electroacupuncture-like stimulation of a peripheral cutaneous nerve. Changes in receptive field sizes in our animal experiments are reversed by administration of naloxone. Two-point thresholds can be reduced significantly by the intravenous administration of naloxone (Velasco et al. 1984).

In all of these simple examples, observed changes in tactile acuity in humans roughly parallel the time courses and extents of changes in the magnitudes and grains of area 3b representations of monkeys undergoing similar "experimental" histories.

Parallels to perceptual changes of body image can also be drawn. Thus, for example, telescoping following amputation (see Haber 1955; Merzenich, Nelson et al. 1984; Teuber et al. 1949) indicates that reorganization of a body image map(s) occurs in these patients. Correction in the body surface image for finger identity following an island pedicle transfer constitutes another example of an alteration in body image representation that parallels reorganization changes recorded in our experiments. Despite this parallelism, we believe it to be most likely that such effects are accounted for by reorganization in somatosensory cortical areas not yet studied with this class of experiment, in part because of the magnitudes of implied representational changes indicated by these recovery phenomena.

In general, it is highly likely that area 3b representational changes account for its fractional part of the acquisition of tactual skill with practice—that the forebrain mechanisms underlying the adaptive changes revealed in these experiments minimally constitute the bases of at least a major neocortical component of learning and memory.

THESE PROCESSES ARE PROBABLY GENERAL IN THE NEOCORTEX

Only a few closely parallel experiments have been conducted in other cortical regions. Nonetheless, they indicate that this use-driven alterability in effective driving inputs is widespread and probably universal in the neocortex. Diamond and Weinberger have described changes in frequency response areas of neurons in auditory cortex generated by classical conditioning that resulted in an increased territorial representation of the frequency of the unconditioned stimulus (Diamond 1985; Weinberger and Diamond 1987). Similar experiments conducted earlier in the motor cortex indicate that there are substantial increases in the territories of representation of conditioned movements (Woody and Engel 1972).

These experiments indicate that with classical conditioning, there is a remodeling of representations in specific cortical areas resulting in larger territories of representation of conditioned responses and conditioning stimuli. In both auditory cortex and motor cortex studies, representational changes paralleled conditioning—i.e., were generated after only a few trials, were extinguishable, and are not accounted for by sensitization.

In the second decade of this century, Sherrington and colleagues (Graham Brown and Sherrington 1912; Layton and Sherrington 1917) noted that motor stimulation "maps" can be substantially altered by surface electrical stimulation. Changes in anthropoids and macaques were especially remarkable. We have repeated this experiment using intracortical stimulation in area 4 in adult rats (Nudo and Merzenich 1987; Fig. 8). Intracortical stimulation at current levels above or well below movement thresholds is highly effective for generating representational changes for movement that are hundreds of microns in extent. The movement initially evoked at the stimulation site comes to be represented over a substantially greater territory after stimulation. Substantial changes are recorded after more than ten minutes of stimulation. Subthreshold effects indicate that induced changes are not dependent upon repetitive movement-selective afferent inputs. These and other ongoing studies in motor representations indicate that movement representations revealed by intracortical microstimulation are highly alterable by use.

We have conducted a number of studies in another somatosensory cortical field: area 1. Its representations were altered after nearly every experimental manipulation described above; changes were very different from those in area 3b, but representational translocations were invariably of at least an equal magnitude (Finkel et al. 1987). As noted earlier, Pons and colleagues recently described a remarkable representational reorganization in the principal somatosensory representation of SII in adult macaques following complete cortical ablation of the hand representations in SI; i.e., following ablation of the principal sources of afferent input into this field (Pons 1987). Changes are on a much greater scale than those recorded in either area 3b or 1. Normal maps of other somatosensory cortical fields and in area 4 in adult monkeys reveal a substantial variability consistent with these representations being shaped idiosyncratically by use (Gould et al. 1986; Pons 1984; Robinson and Burton 1980; see Merzenich 1985; Merzenich et al. 1987).

CONCLUSION; SOME IMPLICATIONS

These studies provide a modified view of the operationally significant features of the neocortex. They demonstrate that excitatory responses of cortical neurons

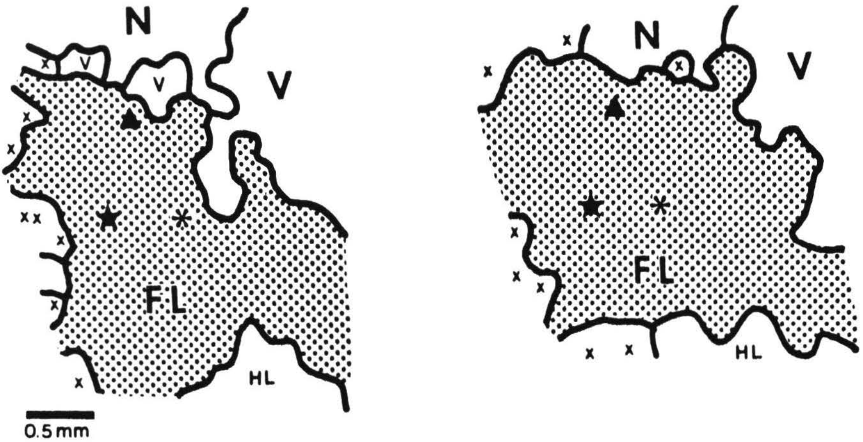


Fig. 8—Group enlargement in the motor cortex as a consequence of intracortical stimulation. After deriving a detailed map of the representation of forelimb movements in area 4 in an adult rat (left), intracortical electrical stimulation (40ms duration 300 pps bursts delivered once/second) was applied in the pyramidal tract neuron levels for a period of three hours. Stimulation was at about two times the threshold current level for evoking forelimb movement. A subsequently defined map (right) revealed an expansion of the forelimb movement representational zone into previously unresponsive cortex (x); into the hindlimb zone (HL); marginally into the zone of representation of the neck (N); and especially into the zone of representation of vibrissal movement (V). Evoked forelimb movements within these expanded zones were not distinguishable from those evoked at the chronic stimulation site. All responses were of a relatively low threshold. Similar distortions of motor maps could be effected in both directions across these representational boundaries, and changes were recorded after stimulation at levels well below those required to evoke any observable movement or EMG response.

are alterable by use by the operation of dynamic intrinsic neocortical mechanisms. By the operation of these mechanisms, countless idiosyncratic forms of distributed, selected inputs can be generated within a given cortical field over a lifetime. Input selection operates for all of the basic anatomically categorized response features of delivered inputs. Considered from the afferent input side alone, input coincidence can strongly influence input selection; coincidence-based input selection is hypothesized to account, in part, for the generation and conservation of local representational order.

There is almost certainly a cognitive side to this machinery as well. Even in the somatosensory koniocortex, input effectiveness is almost certainly modulated as a function of behavioral state. Mechanisms accounting for this modulatory control are still little-studied and not completely understood. Recent studies more strongly implicate an opiate-based system in this modulatory control, apparently coupled to acetylcholine- and norepinephrine-based systems.

Input "selection" or "restriction" is achieved by closely coupled inhibitory and excitatory processes. The full repertoire of selectable inputs is anatomically probably ever-present. Part — but possibly not the full range — of the selectable excitatory repertoire may require no new synapse formation for its expression. The "anatomical map" is crude compared to normally expressed "physiological maps". By its projectional degeneracy, it establishes — and limits — the repertoire of selectable inputs at any given cortical location.

Input selection or restriction is achieved by functional, locally coupled groups of neurons. The extent of overlap of neocortical neuronal groups has not yet been established, but it is believed that they are relatively sharply bounded. They collectively restrict or select a subset of effective excitatory inputs, which dominate the responses of all group members. These functional neuronal groups are almost certainly established, maintained, and altered in the cortex by coincidence-based mechanisms. Groups appear to be dynamic, functional, (not fixed anatomical) entities. They move in the neocortex. Their borders move. They undergo substantial changes in their extents in normal animals, and under special circumstances can enlarge nearly a thousand-fold in extent.

Again, these "functional minicolumn" or "neuronal group" dynamics are not easily reconciled with the predominant historical views of columns or minicolumns as fixed anatomical entities.

We have recently hypothesized that there are probably in-place mechanisms for stabilizing distributed arrays of functional groups and their selected inputs (Merzenich 1987). These hypotheses have yet to be tested.

These adaptive processes probably constitute *the* functional bases of the origins of higher brain functions. It is clear that records of behaviorally significant inputs are "stored" in areas of the cortex in which such inputs do not overtly drive neurons (Merzenich 1987; Merzenich, Jenkins et al. 1984); such stored consequences must be invoked to account for the directed, progressive reshaping of cortical representational detail over time. Representational changes parallel simple perceptual phenomenology and plausibly account for them. Representational changes almost certainly related to learning and the acquisition of skill have been recorded in both sensory and motor cortical areas.

It should be noted that nearly all of the somatosensory experiments described in this brief review were conducted in the koniocortical field, area 3b. This field has the most constrained anatomical distribution of inputs of any somatosensory representation; it is presumably the *least* alterable of the eight or nine or more somatosensory cortical representations in anthropoids. That conclusion is supported by studies of representational plasticity in cortical areas 1 and SII, where representational translocation distance limits are apparently substantially greater than those recorded in 3b. In general, the greater the number of sources of correlatable inputs and the greater the divergence and convergence of their afferent distributions, the greater the possible representational plasticity. Each engaged self-organizing cortical zone makes a field-specific contribution to perception and cognition.

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