

A Histologically Visible Representation of the Fingers and Palm in Primate Area 3b and its Immutability Following Long-term Deafferentations

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An isomorph of the glabrous hand is visible in primary somatosensory cortex (area 3b) of owl monkeys in brain sections cut parallel to the surface and stained for myelin. A mediolateral row of five ovals, separated by myelin-light septa, represents digits and corresponds precisely with cortical sites activated by light touch on individual digits in microelectrode recordings. A number of caudal ovals relate to pads of the palm. A more distinct septum separates the hand from the more lateral face representation. Within the face representation, two large myelin-dense ovals can be identified that are activated by the upper or lower face in a caudo-rostral sequence. Accidental finger loss or dorsal column section, deafferentations that result in reorganization of the physiological map in area 3b, do not alter the morphological map. The proportions for each digit and palm in the morphological map do not vary across normal and deafferented animals. Similar isomorphs were also seen in area 3b of squirrel and macaque monkeys. We conclude that the anatomical isomorph for the body surface representation in area 3b is a reliable reflection of normal cortical organization and may be a common feature of the primate area 3b. The isomorph can provide a reference in studies of somatotopic reorganization.

Introduction

To help construct coherent percepts using inputs from discrete peripheral receptors, information is channeled and maintained in topographical maps of individual receptor sheets. These maps were first described electrophysiologically in somatosensory cortex (Marshall *et al.*, 1937; Penfield and Boldrey, 1937; Adrian, 1941). Surface anatomical features such as sulci and dimples have long been known to distinguish the representational boundaries of digits of the forepaw and other body parts in raccoons and to a lesser extent in other large brained carnivores (Welker and Seidenstein, 1959; see Johnson, 1990 for review). Our understanding of the organization of these maps advanced considerably following the demonstration of a histologically apparent, modular representation of mystacial vibrissae, termed the 'barrel field', in the S1 of mouse in cortical sections stained for Nissl substance (Woolsey and Van der Loos, 1970). Later, isomorphs of other body parts, including subdivisions related to digits of the hand and foot, were described in brain sections processed for cytochrome oxidase or succinic dehydrogenase (Land and Simons, 1985; Dawson and Killackey, 1987; Wallace, 1987; Li *et al.*, 1990; Jain *et al.*, 1995; Waters *et al.*, 1995). Isomorphs of parts of the body in S1 have been found in other mammalian species such as brush tailed possums (Weller, 1972) and moles (Catania and Kaas, 1995; Catania and Kaas, 1997). Modular compartments are also present in subcortical nuclei in the thalamus and medulla (e.g. Belford and Killackey, 1978; Belford and Killackey, 1979; Kaas *et al.*, 1984; Florence *et al.*, 1989; Crockett *et al.*, 1993), and in other sensory systems, especially the visual system (Wong-Riley, 1994). Boundaries of such isomorphs correspond to boundaries of thalamocortical, cortico-cortical and callosal connections (Olavarria *et al.*, 1984;

Koralek *et al.*, 1988; Casagrande and Kaas, 1994). However, such isomorphs have not been demonstrated in the somatosensory cortex of primates, even though the hand area of primates has been intensively studied for decades.

In species where an anatomical isomorph has been seen, there is normally a very precise correlation between the anatomical and physiological maps (e.g. Welker, 1976). However, microelectrode mapping experiments have conclusively established that topography of the physiological maps in S1 is changeable, even in adults, following peripheral deafferentations by nerve damage (Merzenich *et al.*, 1983), amputations (Florence and Kaas, 1995) or spinal injuries (Jain *et al.*, 1997a) in a variety of species (see Kaas, 1994). The deafferented regions of the cortex acquire new receptive fields and start responding to normally innervated skin. However, in adult rats, the S1 barrel field and other morphological structures seem to be relatively stable after deafferentations and reorganizations (McCandlish *et al.*, 1996). Thus, one might ask if morphological maps of primates change with the alterations in the physiological maps.

Here we show that in somatosensory area 3b of owl monkeys there are anatomical isomorphs of individual digits and palmar pads of the hand. In normal monkeys, these isomorphs accurately and consistently reflect the physiological maps of the hand. These isomorphs remain unaltered even after long-standing peripheral or spinal deafferentations that result in extensive reorganizations and novel receptive fields in the deafferented cortex. Such isomorphs may be a common feature of S1 of primates since similar isomorphs were apparent in area 3b of squirrel monkeys and macaque monkeys.

Materials and Methods

Microelectrode recordings were used to identify parts of the hand representation in area 3b in eight hemispheres from seven adult owl monkeys, *Aotus trivirgatus*. Five of these hemispheres had normal inputs from the hand, two had altered inputs due to digit amputations, and four had altered inputs due to transection of the dorsal columns. After mapping, somatosensory cortex was removed, flattened, cut parallel to the surface and processed for myelin. In addition, three hemispheres from three owl monkeys were flattened and processed for myelin without extensive mapping in the hand region. Somatosensory cortex from four hemispheres from three macaque monkeys (two *Macaca mulatta* and one *Macaca nemestrina*) and one hemisphere from a squirrel monkey (*Saimiri sciureus*) was also processed.

Deafferentations

Owl monkeys 95-12 and 95-75 had injured their fingers and these had been amputated for therapeutic reasons by University veterinarians independent of this study. Monkey 95-12 had digit 4 and distal digit 1 (thumb) of the right hand amputated 4 years and 8 months before recordings and perfusion. Monkey 95-75 had digits 3 and 4 of the right hand amputated 3 years and 8 months before this study. In four owl monkeys, the dorsal column afferents were sectioned unilaterally at the

cervical levels 3/4 as part of another study (see Jain *et al.*, 1997a, for details). Somatosensory cortex in these monkeys was mapped 5 days–8 months after the dorsal column section. All animal protocols were reviewed and approved by the Institutional Animal Care and Use Committee and followed NIH guidelines.

Microelectrode Mapping

Standard multiunit microelectrode mapping procedures were used to record from the hand region of primary somatosensory cortex, S1 (area 3b), of owl monkeys (see Jain *et al.*, 1995). Briefly, the animals were anesthetized using a mixture of ketamine hydrochloride (8 mg/kg, i.m.) and xylazine (0.4 mg/kg, i.m.) and surgical levels of anesthesia were maintained using the same anesthetics. After a craniotomy over S1, the dura was reflected and the brain was covered with warm silicone to prevent desiccation. Receptive fields for neurons in the middle layers of cortex were mapped using parylene-coated tungsten microelectrodes (1 MΩ at 1 kHz; Micro Probe Inc.). The electrode penetration points were marked relative to the blood vessels and other surface features on a magnified photograph of the brain surface. In order to delimit receptive fields, the skin was lightly touched with brushes, wooden probes and Semmes–Weinstein filaments. The area of skin that produced responses to minimal stimulation was defined as the minimal receptive field (Merzenich *et al.*, 1983) and marked on diagrams of the body surface. The investigator mapping the receptive fields was unaware of the locations of the electrode in the brain. At the end of recording sessions electrolytic marking lesions were placed at selected sites by passing cathodal current (10 μA for 10 s) to help in relating the electrode penetration sites to the brain sections.

Histology

The animals were killed with a lethal dose of sodium pentobarbital and perfused transcardially with a sequence of buffered saline, 2% paraformaldehyde, and 2% paraformaldehyde containing 10% sucrose. The cortex was separated from the thalamus and flattened between glass slides. The tissue was cryoprotected overnight in 30% buffered sucrose, frozen and cut parallel to the pial surface at 40 or 50 μm on a sliding microtome.

Sections were stained for myelin according to the procedure of Gallyas (1979) with slight modifications. Briefly, the sections were incubated in pyridine and acetic acid (2:1) for 30 min and rinsed three times in 0.5% acetic acid, 3 min each. This was followed by incubation in ammoniacal silver nitrate, and three rinses in 0.5% acetic acid (3 min each). The sections were stained in a solution containing equal amounts of 0.5% sodium carbonate and a mixture of ammonium nitrate (0.2%), silver nitrate (0.2%), tungstosilicic acid (1.0%) and formalin (0.5%), and rinsed several times in deionized water. The contrast was developed in 0.5% potassium ferricyanide and the sections were rinsed again. The major difference in our staining procedure as compared to the conventional method was to overstain the sections until even the lightest parts just turned dark, and then to develop the contrast by destaining in the potassium ferricyanide solution. The development–contrast enhancement cycle was repeated (typically once more) until the desired contrast was obtained. The sections were finally fixed in sodium thiosulfate (0.5%) for 5 min and mounted out of gelatin–alcohol on gelatin-subbed slides. In some cases a series of alternate sections was reacted for cytochrome oxidase (CO) activity by the procedure of Wong-Riley (1979). The CO-dense region previously described as area 3b in owl monkeys (Tootell *et al.*, 1985) corresponds to the myelin-dense region of the present report. However, we found that myelin-stained sections provided more detail of the subdivisions within the hand representation.

To calculate relative areas of digits, palm and total hand isomorphs, the myelin-stained sections were projected using a projection microscope, and outlines of these regions were drawn. Sometimes, outlines were completed by superimposing features from adjacent sections using blood vessels and tissue artifacts for alignment. The drawings were digitized into Pict files using a flatbed scanner. The outlines were converted into Bézier curves using a Macintosh computer and Canvas 3.5.4 software (Deneba Software, Florida). The areas enclosed by these curves were computed using the same software.

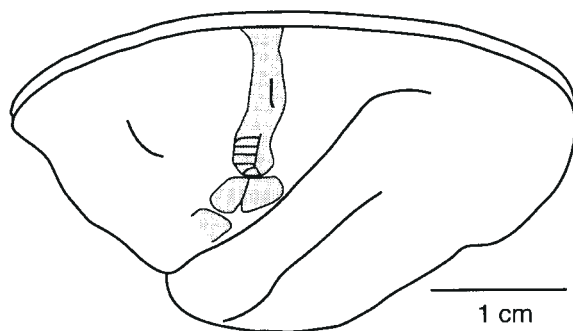


Figure 1. A dorsolateral view of an owl monkey brain showing the location of area 3b (shaded) with outlines of digit representations. Lateral subdivisions correspond to parts of the face representation and the most rostralateral subdivision corresponds to the representation of oral structures. Caudal is to the right.

Results

As in other primates, area 3b of owl monkeys consists of a mediolateral strip in anterior parietal cortex (Fig. 1; Merzenich *et al.*, 1983). Owl monkeys lack a central sulcus so that most of area 3b is exposed on the brain surface. A small dimple, corresponding to the central sulcus, depresses part of area 3b medial to the margin of the hand representation, providing a useful landmark. In sections of flattened cortex cut parallel to the surface and processed for myelin, area 3b appeared as a dark mediolateral band that curved rostrally near its lateral end (Fig. 2). The borders were most prominent in sections through the middle layers of cortex, where the external myelin band of Baillarger is located and the myelin staining is the darkest. The depression of the central dimple persisted in flattened cortex (also, see Tootell *et al.*, 1985) to produce a lightly stained oval of more superficial layers within the darkly stained middle layers of area 3b (Fig. 2). In addition, uneven flattening sometimes made it difficult to see all of the boundaries and internal features of area 3b in a single section. Overall, area 3b was quite distinct from adjoining areas. The dark myelin staining is a characteristic of area 3b in primates (e.g. Krubitzer and Kaas, 1990) and S1 in other mammals (see Krubitzer, 1995).

In the part of area 3b just lateral to the light oval of the central dimple, a number of light septa were clearly apparent (Fig. 2). The most prominent was a horizontal septum which separated the hand representation from the more lateral face representation. Just lateral to the horizontal septum an adjoining, more diffuse vertical septum was apparent (see Fig. 2A for case 95-12; also see Fig. 1). This septum is not so obvious in the less favorable section illustrated for case 95-31 (Fig. 2B). Nevertheless, this short vertical septum was a consistent feature of the surface-view myeloarchitectonic pattern when sections were examined across the depth of the middle layers. This septum separated the face representation in area 3b into two myelin-dark ovals. The results of our microelectrode recordings in six hemispheres indicate that the caudal oval represents the upper lip and face, while the rostral oval represents the lower lip, chin and jaw (also, see Manger *et al.*, 1995). An even more rostral and lateral myelin-dark oval (not shown, but see bottom left corner of Fig. 2A, also see Fig. 1) is devoted to the inputs from the oral cavity. The caudal-most myelin dark oval which extended into the lateral sulcus may be part of area 1.

Close inspection of the hand portion of area 3b (between the bold horizontal septum and the lightly stained region of the dimple) reveals a number of fainter, myelin-light septa (Figs 2–4).

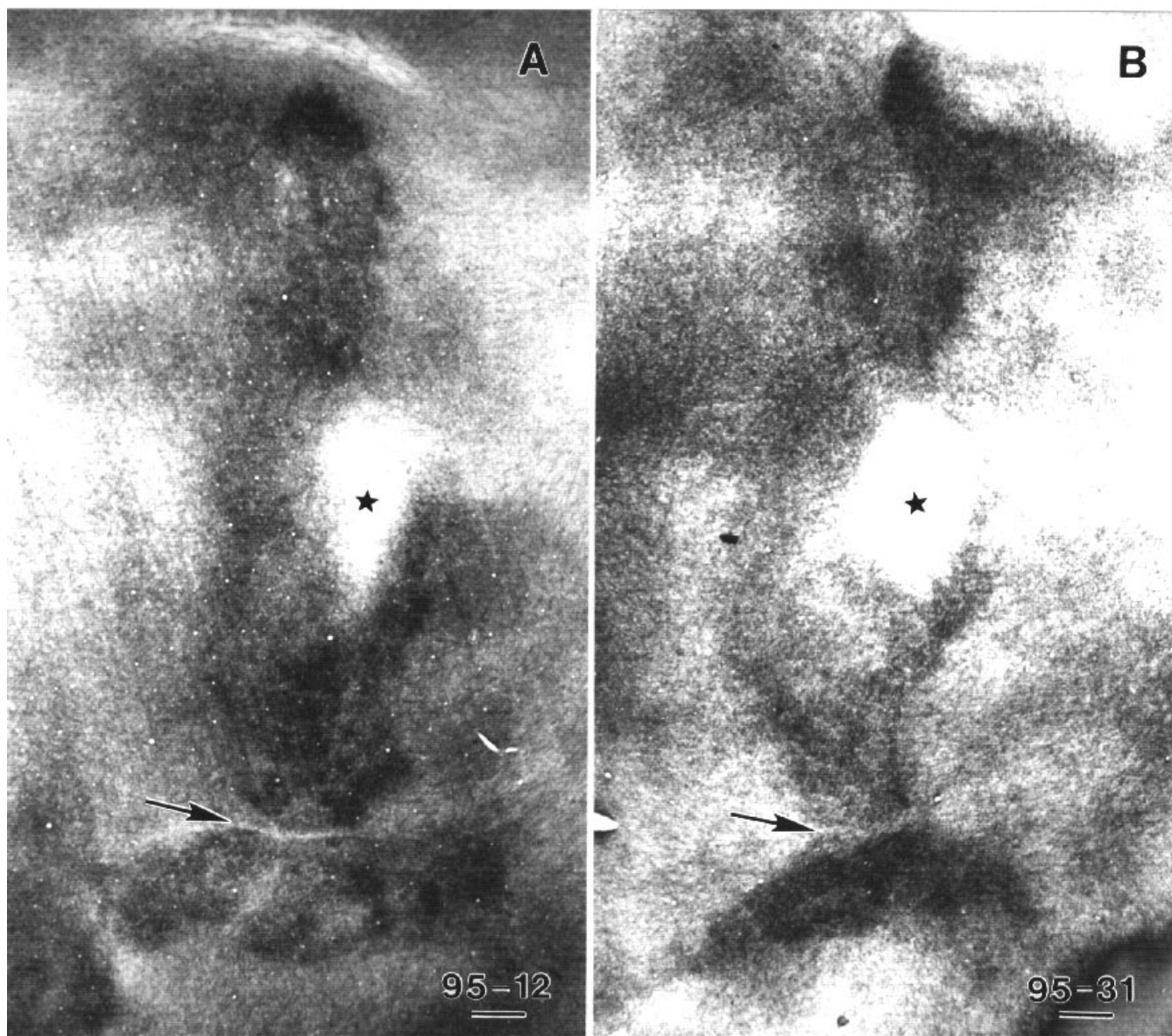


Figure 2. Myelin-stained flattened sections from somatosensory cortices of two owl monkeys 95-12 (A) and 95-31 (B). The myelin dark mediolateral strip corresponds to area 3b (cf. Fig. 1). The lateral representation of face is separated from the more medial hand representation by a myelin-poor septum (arrow). Immediately medial to the hand-face septum, slightly fainter septa between individual digits in the hand representation are also visible. The unstained patch (star) within area 3b is a result of uneven flattening due to the presence of the central dimple. Medial is to the top and rostral to the left. Scale bar, 1 mm.

Rostrally, four narrow 75–100 μm wide septa outlined a medio-lateral row of five myelin dark ovals. These septa outlining the digits were seen in each case, although in many cases the full pattern was most apparent when reconstructed across several brain sections. The caudal half of the hand region of area 3b also had a number of faint septa, but these were more variable.

Microelectrode recordings were made to identify cortical sites responsive to digits and pads of the palm. The physiological map was aligned with the hand isomorph using microlesions made at the end of recording sessions. In two normal owl monkeys (95-75, right hemisphere, Fig. 3C,D, and 95-17, not shown) the rostral row of five ovals correlated with digits D1–D5 in latero-medial sequence. The ovals in the caudal part of the hand representation corresponded with the palm representation. Thus, all the receptive fields in the hand region at all the recording sites precisely matched the isomorphs of individual

digits and the palm seen in the myelin stained sections (see also Fig. 5). Consistent with this discrete representation of each digit, in normal monkeys it is rare to find an electrode penetration site where receptive fields of neurons overlap adjacent digits (Wang *et al.*, 1995). Occasionally we could also discern very faint septa within a digit representation (see Figs 3A, 4A).

Effects of Deafferentations on the Hand Isomorph

We mapped two monkeys with long-standing amputations of one or more digits of the hand. The amputations were performed for veterinary reasons as a treatment for injury. Monkey 95-12 (Fig. 4A) had D4 and distal D1 of the right hand amputated 4 years and 8 months before the mapping experiment and perfusion. In the myelin-stained sections of contralateral somatosensory cortex of this monkey D4 and D1 were clearly delineated from adjacent digits and the more caudal representation of palm. There was no

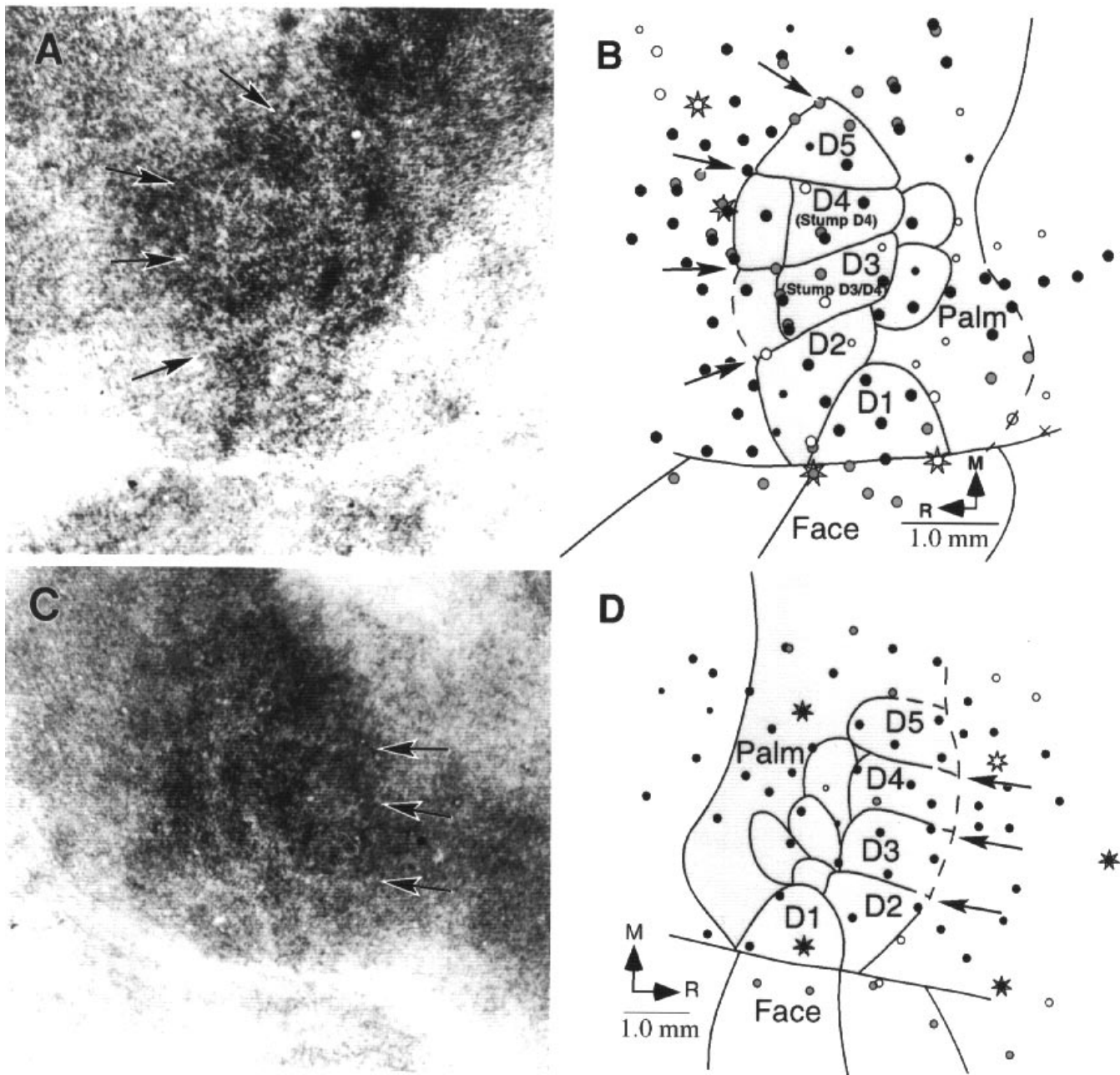


Figure 3. Higher-magnification photomicrographs of hand isomorphs in area 3b of left (A) and right (C) hemisphere in the myelin-stained flattened cortex of owl monkey 95-75. The septa and boundaries of the area 3b in (A) and (C) are outlined in (B) and (D) respectively. The arrows point to some of the corresponding interdigital septa. The dots in (B) and (D) indicate electrode penetrations sites. Solid dots show penetrations with neurons responding to glabrous skin, gray dots, to the deflection of hairs. Sizes of dots indicate qualitative magnitude of the response, with larger dots indicating more vigorous responses with lower stimulus thresholds. Stars show the locations of microlesions used to overlay the electrophysiological map on the anatomical map. As the lesions are small, they are most obvious only in one or two brain sections and are not visible in sections shown in (A) or (C). This monkey had D3 and D4 of the right hand amputated 3 years and 8 months before mapping and being killed. The responses due to plastic reorganizations of the physiological map in this part of cortex are indicated in parenthesis in (B). Note that there is no effect on the isomorphs of individual digits (A). Maps shown in (C) and (D) are from the normal contralateral hemisphere. The rostral part of the digit representation is not visible in the section shown in (C) due to imperfect tissue flattening. Scale bars in the right column are also valid for the corresponding figures in the left column.

obvious reduction in the size of the isomorphs of amputated digits as compared to other digits or any apparent expansion of adjacent digits or palm. Electrophysiological recordings showed that the distal part of the morphological representation of D4 responded to the stimulation of distal D3, and the middle and proximal parts responded to the stimulation of the third palmar pad and the stump of D4 (Fig. 4B). The region that corresponded

to the isomorph of distal D1 responded to the stimulation of remaining D1. No recording sites unresponsive to the somatic stimulation were seen.

The other monkey, 95-75, had D3 and D4 of the right hand amputated 3 years and 8 months before the final mapping experiment. The myelin staining showed a clear representation of both D3 and D4, well separated from adjacent digits, without

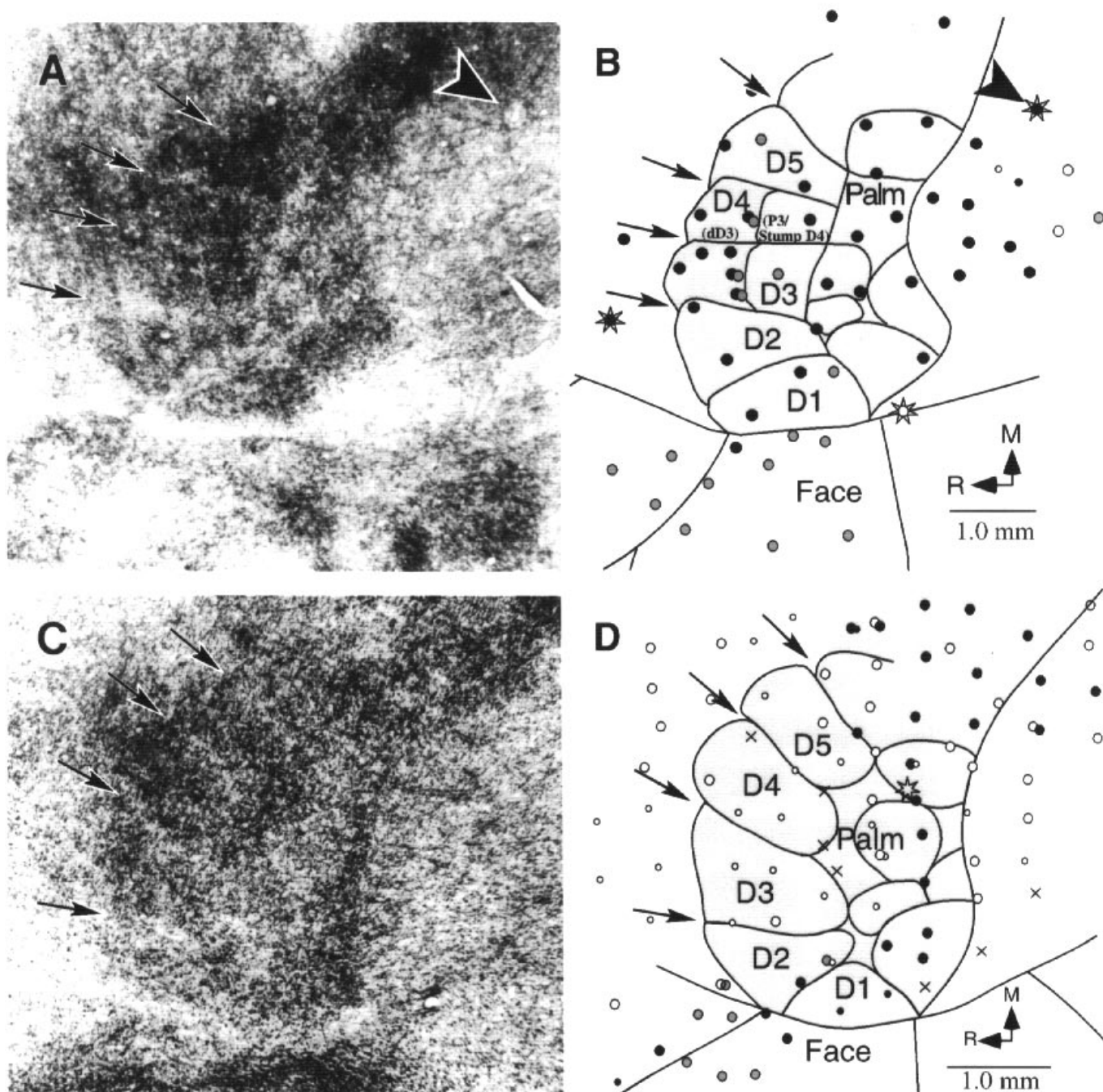


Figure 4. Higher-magnification photomicrographs of hand isomorphs in area 3b of two owl monkeys (A, C). Conventions as in Figure 3. Owl monkey 95-12 (A) had distal D1 and D4 amputated 4 years 8 months before perfusion. Despite reorganization of the physiological map shown in (B), there is no effect of the amputations on the anatomical representation of these digits. Owl monkey 95-31 (C) had partial section of the contralateral dorsal columns at the C3/C4 level 6 months before being killed. The physiological map in this animal was highly abnormal (see Results) but the individual digit isomorphs are still intact. One of the microlesions used to align electrophysiological and anatomical maps is clearly apparent in (A) (see arrowheads in upper right corners of A and B).

any obvious reduction in size as compared to other digits (Fig. 3A). The electrophysiological recordings showed that the cortical zones representing missing digits responded to the stimulation of the stumps of D3 and D4 (Fig. 3B). Again, no unresponsive penetration sites were seen, suggesting a complete reactivation of the deafferented cortex (while Merzenich *et al.* (1984) previously reported an incomplete reactivation following amputation of two adjacent digits, the recovery period for our owl monkeys was much longer). The reorganization of the

cortex was not accompanied by any obvious changes in the morphological representation of individual digits in the middle layers of area 3b. In addition, in both these cases, physiological representations of the intact digits and palm were completely congruent with their isomorphs revealed in the myelin-stained sections.

We also investigated the effect of dorsal column section on the hand isomorph in four owl monkeys. After partial or complete unilateral dorsal column section at upper cervical (C3/C4) levels,

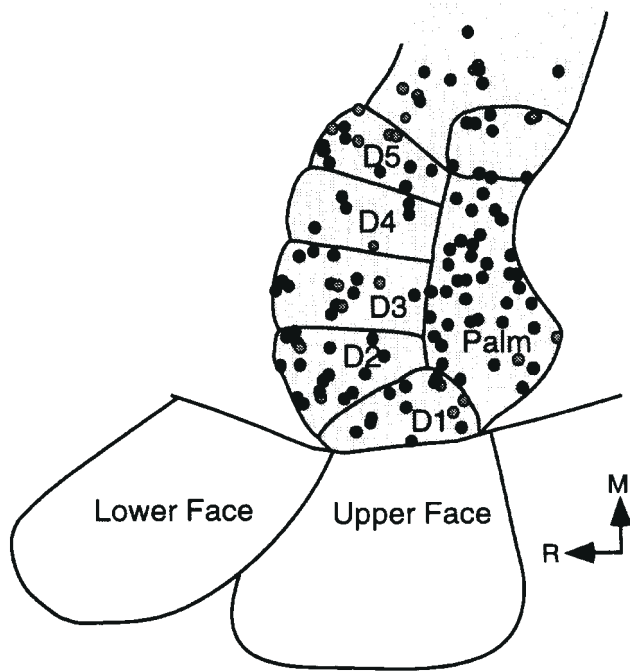


Figure 5. A summary of all the recording sites from four hemispheres of owl monkeys overlaid on a standard outline of the hand isomorph. The sites included are from two normal hemispheres (95-17 and 95-75 right hemisphere), and the parts of the isomorph corresponding to the normal hand in two monkeys with digit amputations (95-12 and 95-75 left hemisphere). Sites were placed in the standard outline relative to their position within digit ovals, the palm strip or more medial cortex in each case. All receptive fields for neurons in the normal cortex were congruent with the hand isomorph.

the electrophysiological maps of these animals were highly abnormal as described in detail elsewhere (Jain *et al.*, 1997a). Monkey 95-31 survived for 6 months after an incomplete dorsal column section. In this animal, the normal hand cortex responded to the few remaining dorsal column inputs and to the stimulation of chin. However, the isomorph of the hand representation shows clear digit and palmar subdivisions (Fig. 4C,D). There was no degradation of the isomorph or obliteration of the septa delineating anatomical subdivisions of the hand or the hand-face border. Monkey 95-67 (not shown) survived for 5 days after dorsal column section. In this monkey, large lateral portions of the hand representation were unresponsive to peripheral stimulation. A third monkey with incomplete dorsal column section (95-15, not shown) survived for 36 days and had complete reactivation with abnormal somatotopy in the hand region of area 3b. In both of these cases the anatomical isomorph of the hand representation was intact. Finally, one owl monkey (95-87, not shown) had complete transection of the dorsal column afferents. After eight months of recovery the hand cortex in area 3b responded to stimulation of the chin, except the medial portion where responses to stimulation of both the chin and the arm were seen. In this animal also the myeloarchitecture revealed an intact hand isomorph.

The areas of isomorphs of individual digits or palm relative to the area of representation of whole hand for the experimental cases in which complete hand isomorph was visible in a single section are shown graphically in Figure 6A. The relative area of the hand cortex devoted to each digit and palm in animals with reorganized cortex is comparable to that in normal animals, and there is no apparent change that relates to the type or extent of

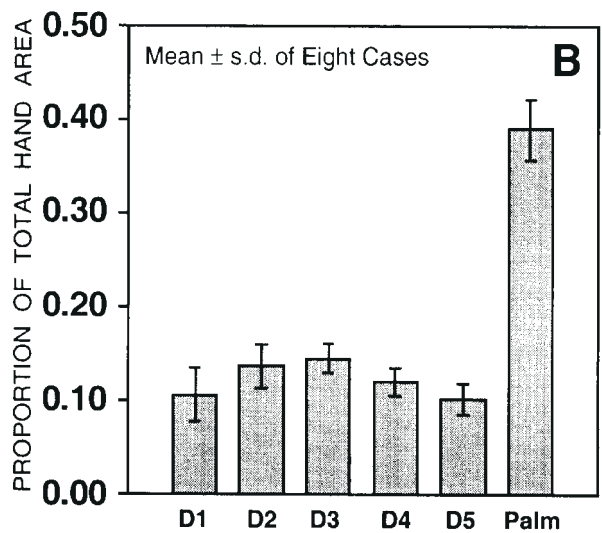
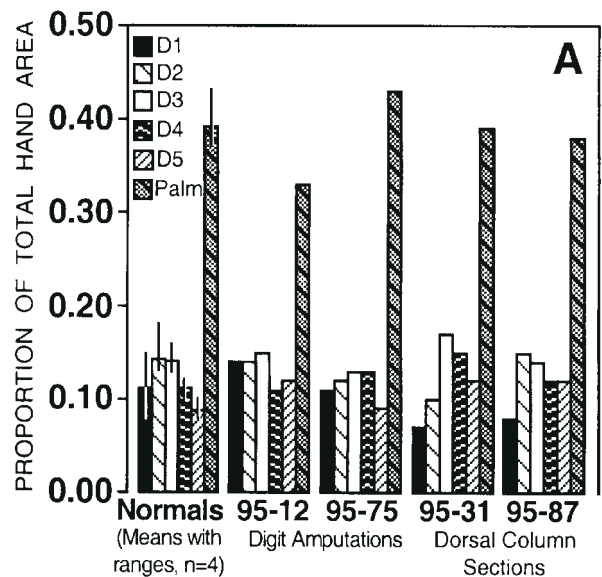


Figure 6. (A) The areas of the isomorphs of each digit and palm as a fraction of total hand area in four normal owl monkeys (95-17, 97-40, 97-53 and 97-97; the bars represent mean values, and the lines on the bars indicate the range), two owl monkeys with digit amputations on right hands (95-12 and 95-75, see Figs 4A and 3A), one owl monkey with partial right dorsal column section (95-31, see Fig. 4C) and one owl monkey with complete left dorsal column section (95-87). The relative sizes of digit and palm isomorphs are similar across cases, indicating no obvious effect of digit loss or dorsal column section. (B) Mean area ($\pm$ SD) of anatomical representation of each digit and palm as a fraction of total hand representation in all the eight cases shown in (A).

reorganization of the physiological map of the hand. It therefore appears that deafferentation of cortex by digit amputation or dorsal column section has no obvious effect on the isomorph of the hand in the somatosensory area 3b, even though the electrophysiological response pattern shows a completely reorganized cortex in the same region. The anatomical boundaries of the individual digits remain intact and clear.

Consistent and Variable Features of the Anatomical Hand Representation

In all the cases examined, the myelin-poor septum at the hand-face border was more distinct than the septa separating the individual digit representations. Isomorphs of D3, D4 and D5

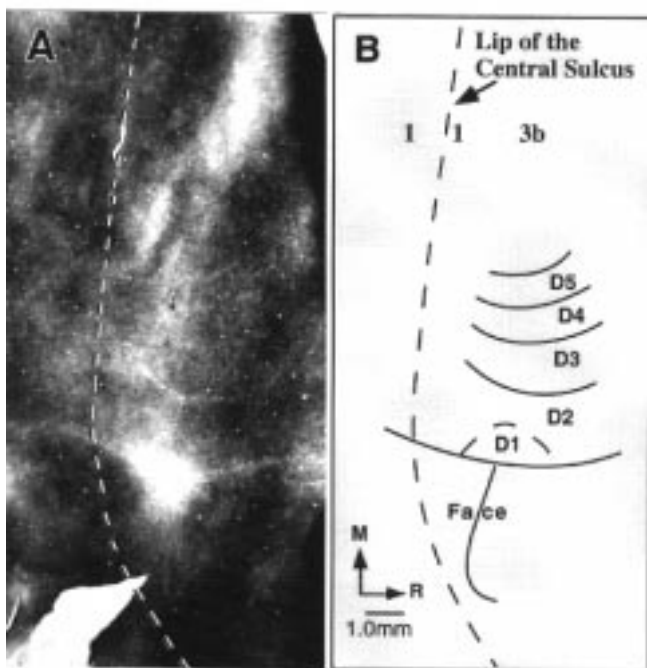


Figure 7. (A) A myelin-stained section through area 3b from the flattened cortex of a macaque monkey. (B) An outline of the section in (A) showing a septum at the hand-face border, interdigital septa and part of the septum subdividing the face representation. Digit 1 is not clearly visible in this particular section. Digit tips are indistinct because they occur at the depth of the central sulcus and extreme curvature of cortex leads to imperfections in the flattening. The dashed line corresponds to the position of the caudal lip of the central sulcus. Expected locations of areas 1 and 3b are indicated.

were more rectangular, with the interdigital septa separating digits D2–D5 forming nearly straight and parallel borders. D2 was conical with a narrower caudal end and a wider rostral end. D1 was consistently semicircular. The caudal end of D1 extended more caudally as compared to other digits. The rostro-lateral end of the D2 isomorph (distal digit representation) generally extended close to the hand-face border. The septa in the palmar region were variably apparent. Depending on the case, we could differentiate between three and seven subdivisions in the palm region, but we did not relate them individually to the pads of the palm.

Relative Sizes of Hand Subdivisions

We calculated area of representation of each digit or palm relative to total area of the hand isomorph in the cases where we could clearly delineate most of the isomorph in a single section. Absolute sizes of representations were not considered in order to avoid variations due to differences in brain size and differential shrinkage during perfusion, staining and mounting. The relative sizes of representation of hand subdivisions showed little variability across animals (Fig. 6B), with somewhat more variation in the representation of D1 and the palm as compared to other digits. The palm occupied ~39% of total hand representation, and the digits between 11% (D1) and 15% (D3). We calculated means across these cases even though some animals had peripheral or spinal deafferentations, since there was no obvious effect of the deafferentation on the isomorphs (see above).

Isomorph of the Body in Macaque and Squirrel Monkeys

We examined two other primate species to determine if the hand isomorph is a peculiar feature of owl monkeys or is present in other primates as well. Sections of the flattened cortex from four hemispheres of three macaque monkeys were stained for myelin. In these sections a myelin-poor septum separating hand and face regions of the cortex was clearly visible (Fig. 7A). Even though we did not map the cortex in these cases, the location of this septum near the tip of the intraparietal sulcus matched the expected location of the hand-face border in the macaque brain (Florence and Kaas, 1995). Medial to this myelin-poor septum at the hand-face border, there were fainter septa, presumably separating representations of individual digits (Fig. 7). The width of the digits (~1.0–1.5 mm) in the isomorph matched with the width of digits calculated in the physiological mapping studies of macaque area 3b (see Nelson *et al.*, 1980; Pons *et al.*, 1987). As macaque area 3b is located on the posterior bank of the central sulcus, it was more difficult to clearly visualize the digit tips and palmar regions of the isomorphs due to extreme curvature of the cortex in these regions. Nevertheless, the macaque hand isomorph was strikingly similar to the owl monkey hand isomorph. The hand isomorph was also seen in one hemisphere from a squirrel monkey (not shown).

In the material from macaque cortex we could also make out a medio-lateral septum subdividing the face region (Fig. 7). On the basis of the published mapping data (Nelson *et al.*, 1980; see however Manger *et al.*, 1996) and the similarities with owl monkeys' isomorph, it is reasonable to conclude that the rostral myelin dark oval represents chin and lower lip and the caudal oval represents the upper lip and face.

Discussion

The main finding of the present report is that an isomorph of the hand is visible in area 3b of monkeys in brain sections cut parallel to the surface and stained for myelin. The isomorph is not altered by long periods of sensory deprivations that produce reorganizations of the physiologically determined representation. The isomorph allows individual variability in the hand representation to be examined in a new and highly accurate way and allows experimentally produced reorganization of the hand maps to be precisely evaluated relative to the previously existing normal maps in the same animals. The septa in the isomorph may emerge in development between populations of neurons with different patterns of correlated activation.

The Prevalence and Significance of Somatotopic Isomorph

Primary somatosensory cortex and subcortical relays have been shown to be parcellated into anatomically distinct regions related to body parts in a number of species. Perhaps the best-known example is the so-called barrel field of primary somatosensory cortex of rats and mice, first described by Woolsey and Van der Loos (1970). In the barrel field, clusters of neurons are separated by cell-poor septa, with each cluster or 'barrel' being activated largely by a single, specific vibrissa on the snout. The barrels appear as dark ovals in brain sections processed for myelin (e.g. Krubitzer, 1995), cytochrome oxidase (e.g. Wallace, 1987), or succinic dehydrogenase (Dawson and Killackey, 1987; Wallace, 1987), and at some developmental stages acetylcholinesterase (Schlagger and O'Leary, 1994) or serotonin (Leslie *et al.*, 1992). Such morphological divisions are not confined to the representation of mystacial vibrissae, but all separate regions of the body, including other vibrissae and pads

of the feet, can be visualized (Dawson and Killackey, 1987; Waters *et al.*, 1995).

Similar isomorphs have been described in the primary somatosensory cortex (S1) of a variety of small, smooth-brained mammals, including the brush-tailed possums (Weller, 1972), a range of rodent species (Woolsey *et al.*, 1975), moles (Catania and Kaas, 1995; Catania and Kaas, 1997) and platypus (Krubitzer *et al.*, 1995). It was because of these anatomical markers of somatotopy that rodents have been such valuable subjects for further studies of the somatosensory system.

In primates, morphological distinctions between the representations of the digits have not been reported before, apparently because they are narrow and somewhat faint even in surface-view preparations, which have not been commonly examined in primates. However, the larger septum between the representations of the hand and face has been noted before in marmosets (Krubitzer and Kaas, 1990), where it has been shown to be a zone of callosal connections, and in macaques (Krubitzer, 1995). Here we described septa separating representations of the hand and face, as well as individual digits, in owl monkeys, squirrel monkeys and macaque monkeys, and postulate that they will be found in other primates, perhaps even in humans and apes. However, such septa may be less distinct and more difficult to visualize in large-brained primates with a more complex sulcal pattern. A septum separating the representation of the hand from the face in the ventroposterior nucleus of the thalamus has long been recognized in many mammals (see Jones, 1985), and it serves as a basis for distinguishing the ventroposterior lateral from the ventroposterior medial subdivisions (nuclei).

The septa are also found in the lateral geniculate nucleus of the visual system, where they separate layers receiving inputs from different eyes, and portions of layers with non-adjacent inputs from two sides of the optic disc of the contralateral retina (Kaas *et al.*, 1973). In both visual and somatosensory systems, the septa correspond to discontinuities in the receptor sheets. Such discontinuities in the receptor sheets may lead to sharp disruptions in the correlations of the activity patterns induced by peripheral afferents across populations of neurons during development, leading to the loss of synapses and the formation of septa (see Meister *et al.*, 1991). Septa may be subsequently invaded by later maturing pathways, such as the corpus callosum. We do not yet know at what stage of development the isomorph of the hand emerges in the cortex of monkeys, or if it can be altered during critical stages of development by peripheral manipulations, as the barrel field of rats (Belford and Killackey, 1980; Killackey and Dawson, 1989).

In rats, the cortical barrels receive thalamocortical inputs from the ventroposterior nucleus while the surrounding septa receive projections from the medial division of the posterior thalamic complex (Koralek *et al.*, 1988) and via corpus callosum (Olavarria *et al.*, 1984). Thus, the barrels and septa form different information-processing units. While the hand portion of area 3b of monkeys has only very sparse callosal connections (e.g. Killackey *et al.*, 1983), a detailed analysis might reveal that the few callosal connections that do exist are concentrated in the interdigital septa. As in the rat barrels, the spread of thalamocortical arbors might be restricted to a single digit isomorph. The terminal arbors of thalamocortical axons in layer 4 of the hand region of area 3b in owl monkeys range from 100 to 900 μm in diameter (Garraghty *et al.*, 1989), a range compatible with the restriction of arbors to single-digit isomorphs. We also predict that intrinsic connections will be denser within than across digit ovals, and that the hand-face

septum will be crossed by few if any intrinsic axons. Feedback connections from higher-order areas may be most concentrated in septa, as might the modulating inputs from the anterior pulvinar. Thus, the discovery of a visible correlate of the hand representation in S1 of monkeys suggests a host of subsequent studies.

A notable feature of the anatomical isomorph of the hand is that it does not seem to include specified locations for the representation of dorsal hairy skin of the hand. In normal owl monkeys, dorsal skin activates few variably located recording sites (Merzenich *et al.*, 1987). Sparser inputs to cortex, when mismatched with the dominant pattern, seem to occupy only small regions of cortex in a variable manner. For example, there is a patchy distribution of weaker cortical inputs from the ipsilateral eye in albino monkeys (Guillery *et al.*, 1984), and in parts of area 17 representing paracentral and peripheral vision in normal monkeys (e.g. Florence and Kaas, 1992). We suggest that the hand region of cortex is normally dominated by the more densely innervated and possibly more stimulated glabrous surface of the hand so that the dorsal hand inputs fail to capture distinct continuous territories. An important goal in future experiments will be to better reference the representations of the dorsal skin in the isomorph.

Anatomical Isomorph and Individual Variability

Physiologically derived maps of the hand have been described as quite variable across normal individual owl and squirrel monkeys (Merzenich *et al.*, 1987). In contrast, the myelin staining shows that the proportions of the hand representation devoted to individual digits and palm are highly similar across our sample of individuals. There are several possible reasons for such differences in results. First, the morphological map probably emerges early in cortical development and stabilizes at a time when environmental influences and neural activity patterns are likely to be similar across individuals. In contrast, the physiological map is mutable throughout life. The receptive fields of neurons can be changed with experience (Recanzone *et al.*, 1992; Wang *et al.*, 1995), and may change in the mature animals as they use their hand in individually idiosyncratic ways. We suggest that the morphological map changes little, if at all, after maturation. It is also possible that our small sample of cases does not adequately reflect the true variability of the anatomical map. A larger population of owl monkeys may vary more in developmental histories or in genetic specification of anatomical features of the map.

Another source of variation in brain maps relates to the limitations of the mapping method. Accuracy of physiological maps depends on the density of recording sites, since the borders are estimated. Our physiological maps also allow interpretations of somatotopic boundaries that are in variance with the morphological maps. However, our physiological data from normal owl monkeys and representations that relate to normal parts of the hand in deafferented owl monkeys were always compatible with the morphological maps. Thus, the physiological maps may prove to be highly congruent with the morphological maps when they are directly examined for correspondences, and the variation due to technical limitations may be the only significant source of difference between the two types of maps in normal monkeys. Nevertheless, the relative sizes of the physiological representations of individual digits reported by Merzenich *et al.* (1987), when averaged, are similar to those seen by us in the hand isomorph, including the observation that the territory of digit 1 shows the most variation.

We conclude that morphological representations provide a highly accurate way of studying individual variability across members of a species, and variability across different primate species. They also make it possible to accurately correlate the receptor densities in digits with their cortical territories and to determine if disproportionate cortical magnification occurs (see Catania, 1995).

Anatomical Isomorph and Map Reorganization

The present results show that the loss of one or more digits, or deafferentations by section of the dorsal columns of the spinal cord, do not alter the cortical isomorphs, even though the physiological maps are reorganized as expected (Florence *et al.*, 1997). The mechanisms for the cortical reorganizations are not completely understood, and they probably differ according to the kind of peripheral deafferentation (Jain *et al.*, 1997b). Experience-dependent changes in the responsiveness of cortical neurons to a non-dominant whisker in the barrel field of rats seem to depend on the strengthening of synapses of intrinsic cortical connections already in place (Armstrong-James *et al.*, 1994), while reorganizations after some types of deprivations appear to utilize the growth and extension of intrinsic cortical connections (Darian-Smith and Gilbert, 1994). In monkeys with amputation of the hand, sprouting of preserved inputs from the upper arm into denervated parts of the cuneate nucleus of the brain stem accounts for some of the reactivation (Florence and Kaas, 1995). Whatever the mechanisms invoked, the persistence of the cortical isomorph during long-term deprivations suggests that any alterations in cortical connections that occur are not extensive enough to appreciably degrade the image. Furthermore, certain kinds of reorganizations may be limited by the anatomical boundaries of the digit representations. For example, extensive stimulation of a small region of the digit during behavioral training in owl monkeys leads to the expansion of the representation of that region of skin in the cortex without any increase in overall extent of representation of the stimulated digit (Recanzone *et al.*, 1992). In addition, the preservation of the cortical isomorph may reflect preserved thalamocortical and intrinsic cortical connections that allow the original map to be restored after somatotopic reorganization. For example, deactivating part of the hand cortex in area 3b by crushing the median nerve results in a reorganized map of the deafferented parts of the hand cortex, but the normal pattern of the hand representation is completely restored after nerve regeneration (Wall *et al.*, 1983). We propose that the morphological map defines the normal map for each animal. This map provides a substrate that allows the altered map to revert and restore normal somatic perception after abnormal peripheral stimulations cease and normal inputs resume.

Notes

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References

Adrian ED (1941) Afferent discharges to the cerebral cortex from peripheral sense organs. *J Physiol* 100:159–191.
 Armstrong-James M, Diamond ME, Ebner FF (1994) An innocuous bias in whisker use in adult rats modifies receptive fields of barrel cortex neurons. *J Neurosci* 14:6978–6991.
 Belford GR, Killackey HP (1978) Anatomical correlates of the forelimb in

the ventrobasal complex and cuneate nucleus of the neonatal rat. *Brain Res* 158:450–455.
 Belford GR, Killackey HP (1979) The development of vibrissae representation in subcortical trigeminal centers of the neonatal rat. *J Comp Neurol* 188:63–74.
 Belford GR, Killackey HP (1980) The sensitive period in the development of the trigeminal system of the neonatal rat. *J Comp Neurol* 193:335–350.
 Casagrande VA, Kaas JH (1994) The afferent, intrinsic, and efferent connections of primary visual cortex in primates. In: *Cerebral cortex*, vol. 10: Primary visual cortex in primates (Peters A and Rockland KS, eds), pp. 201–259. New York: Plenum Press.
 Catania KC (1995) Magnified cortex in star-nosed mole. *Nature* 375:453–454.
 Catania KC, Kaas JH (1995) Organization of the somatosensory cortex of the star-nosed mole. *J Comp Neurol* 351:549–567.
 Catania KC, Kaas JH (1997) Organization of somatosensory cortex and distribution of corticospinal neurons in the eastern mole (*Scalopus aquaticus*). *J Comp Neurol* 378:337–353.
 Darian-Smith C, Gilbert CD (1994) Axonal sprouting accompanies functional reorganization in adult cat striate cortex. *Nature* 368:737–740.
 Dawson DR, Killackey HP (1987) The organization and mutability of the forepaw and hind paw representations in the somatosensory cortex of neonatal rat. *J Comp Neurol* 256:246–256.
 Florence SL, Kaas JH (1992) Ocular dominance columns in area 17 of old world macaque and talapoin monkeys: complete reconstructions and quantitative analyses. *Vis Neurosci* 8:449–462.
 Florence SL, Kaas JH (1995) Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. *J Neurosci* 15:8083–8095.
 Florence SL, Jain N, Kaas JH (1997) Plasticity of somatosensory cortex in primates. *Seminars Neurosci* 9:3–12.
 Gallyas F (1979) Silver staining of myelin by means of physical development. *Neurol Res* 1:203–209.
 Garraghty PE, Pons TP, Sur M, Kaas JH (1989) The arbors of axons terminating in middle cortical layers of somatosensory area 3b in owl monkeys. *Somatosens Mot Res* 6:401–411.
 Guillery RW, Hickey TL, Kaas JH, Felleman DJ, Debruyn EJ, Sparks DL (1984) Abnormal central visual pathways in the brain of an albino green monkey (*Cercopithecus aethiops*). *J Comp Neurol* 226:165–183.
 Jain N, Florence SL, Kaas JH (1995) Limits on plasticity in somatosensory cortex of adult rats: hindlimb cortex is not reactivated after dorsal column section. *J Neurophysiol* 73:1537–1546.
 Jain N, Catania KC, Kaas JH (1997a) Deactivation and reactivation of somatosensory cortex after dorsal spinal injury. *Nature* 386:495–498.
 Jain N, Florence SL, Kaas JH (1997b) Reorganization of somatosensory cortex after nerve and spinal cord injury. *News Physiol Sci* (in press).
 Johnson JI (1990) Comparative development of somatic sensory cortex. In: *Comparative structure and evolution of cerebral cortex*, Part II (Jones EG and Peters A, eds), pp. 335–449. New York: Plenum Press.
 Jones EG (1985) *The thalamus*. New York: Plenum Press.
 Kaas JH (1994) The reorganization of sensory and motor maps in adult mammals. In: *The cognitive neurosciences* (Gazzaniga MS, ed.), pp. 51–71. Cambridge, MA: MIT Press.
 Kaas JH, Guillery RW, Allman JM (1973) Discontinuities in the dorsal lateral geniculate nucleus corresponding to the optic disc: a comparative study. *J Comp Neurol* 147:163–180.
 Killackey HP, Dawson DR (1989) Expansion of the central hindpaw representation following fetal-forelimb removal in rats. *Eur J Neurosci* 1:210–221.
 Killackey HP, Gould III HJ, Cusick CG, Pons TP, Kaas JH (1983) The relation of corpus callosum connections to architectonic fields and body surface maps in sensorimotor cortex of new and old world monkeys. *J Comp Neurol* 219:384–419.
 Koralek KA, Jensen KF, Killackey HP (1988) Evidence for two complementary patterns of thalamic input to the rat somatosensory cortex. *Brain Res* 463:346–351.
 Krubitzer L (1995) The organization of neocortex in mammals: are species differences really so different. *Trends Neurosci* 18:408–417.
 Krubitzer LA, Kaas JH (1990) The organization and connections of somatosensory cortex in marmosets. *J Neurosci* 10:952–974.
 Krubitzer L, Manger P, Pettigrew J, Calford M (1995) Organization of

- somatosensory cortex in monotremes: in search of the prototypical plan. *J Comp Neurol* 351:261–306.
- Land PW, Simons DJ (1985) Metabolic activity in SmI cortical barrels of adult rats is dependent on patterned sensory stimulation of the mystacial vibrissae. *Brain Res* 341:189–194.
- Leslie MJ, Bennett-Clarke CA, Rhoades RW (1992) Serotonin 1B receptors form a transient vibrissa-related pattern in the primary somatosensory cortex of the developing rat. *Dev Brain Res* 69:143–8.
- Li X-G, Florence SL, Kaas JH (1990) Areal distributions of cortical neurons projecting to different levels of the caudal brain stem and spinal cord in rats. *Somatosens Mot Res* 7:315–335.
- Manger PR, Woods TM, Jones EG (1995) Representation of the face and intraoral structures in area 3b of the squirrel monkey (*Saimiri sciureus*) somatosensory cortex, with special reference to the ipsilateral representation. *J Comp Neurol* 363:597–607.
- Manger PR, Woods TM, Jones EG (1996) Representation of face and intra-oral structures in area 3b of macaque monkey somatosensory cortex. *J Comp Neurol* 371:513–521.
- Marshall WH, Woolsey CN, Bard P (1937) Cortical representation of tactile sensibility as indicated by cortical potentials. *Science* 85:388–390.
- McCandlish CA, Li CX, Waters RS, Howard EM (1996) Digit removal leads to discrepancies between the structural and functional organization of the forepaw barrel subfield in layer IV of rat primary somatosensory cortex. *Exp Brain Res* 108:417–426.
- Meister M, Wong ROL, Baylor DA, Shatz CJ (1991) Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina. *Science* 252:939–943.
- Merzenich MM, Kaas JH, Wall J, Nelson RJ, Sur M, Felleman D (1983) Topographic reorganization of somatosensory cortical areas 3B and 1 in adult monkeys following restricted deafferentation. *Neuroscience* 8:33–55.
- Merzenich MM, Nelson RJ, Stryker MP, Cynader MS, Schoppmann A, Zook JM (1984) Somatosensory cortical map changes following digit amputation in adult monkeys. *J Comp Neurol* 224:591–605.
- Merzenich MM, Nelson RJ, Kaas JH, Stryker MP, Jenkins WM, Zook JM, Cynader MS, Schoppmann A (1987) Variability in hand surface representations in areas 3b and 1 in adult owl and squirrel monkeys. *J Comp Neurol* 258:281–296.
- Nelson RJ, Sur M, Felleman DJ, Kaas JH (1980) Representation of the body surface in postcentral parietal cortex of *Macaca fascicularis*. *J Comp Neurol* 192:611–643.
- Olavarria J, Van Sluyters RC, Killackey HP (1984) Evidence for the complementary organization of callosal and thalamic connections within rat somatosensory cortex. *Brain Res* 291:364–368.
- Penfield W, Boldrey E (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 60:389–443.
- Pons TP, Wall JT, Garraghty PE, Cusick CG, Kaas JH (1987) Consistent features of the representation of the hand in area 3b of macaque monkeys. *Somatosensory Res* 4:309–331.
- Recanzone GH, Merzenich MM, Jenkins WM, Grajski KA, Dinse HR (1992) Topographic reorganization of the hand representation in cortical area 3b of owl monkeys trained in a frequency-discrimination task. *J Neurophysiol* 67:1031–1056.
- Schlagger BL, O'Leary DDM (1994) Early development of the somatotopic map and barrel patterning in rat somatosensory cortex. *J Comp Neurol* 346:80–96.
- Tootell RBH, Hamilton SL, Silverman MS (1985) Topography of cytochrome oxidase activity in owl monkey cortex. *J Neurosci* 5:2786–2800.
- Wall JT, Felleman DJ, Kaas JH (1983) Recovery of normal topography in the somatosensory cortex of monkeys after nerve crush and regeneration. *Science* 221:771–773.
- Wallace MN (1987) Histochemical demonstration of sensory maps in the rat and mouse cerebral cortex. *Brain Res* 418:178–182.
- Wang X, Merzenich MM, Sameshima K, Jenkins WM (1995) Remodeling of hand representation in adult cortex determined by timing of tactile stimulation. *Nature* 378:71–75.
- Waters RS, Li CX, McCandlish CA (1995) Relationship between the organization of the forepaw barrel subfield and the representation of the forepaw in layer IV of rat somatosensory cortex. *Exp Brain Res* 103:183–197.
- Welker C (1976) Receptive fields of barrels in the somatosensory neocortex of the rat. *J Comp Neurol* 166:173–190.
- Welker WI, Seidenstein S (1959) Somatic sensory representation in the cerebral cortex of the raccoon (*Procyon lotor*). *J Comp Neurol* 111:464–501.
- Weller WL (1972) Barrels in somatic sensory neocortex of the marsupial *Trichosurus vulpecula* (brush-tailed possum). *Brain Res* 43:11–24.
- Wong-Riley MTT (1979) Changes in the visual system of monocularly sutured or enucleated cats demonstrable with cytochrome oxidase histochemistry. *Brain Res* 171:11–28.
- Wong-Riley MTT (1994) Primate visual cortex: dynamic metabolic organization and plasticity revealed by cytochrome oxidase. In: Cerebral cortex, vol. 10: Primary visual cortex in primates (Peters A, Rockland KS, eds), pp. 141–200. New York: Plenum Press.
- Woolsey TA, Van der Loos H (1970) The structural organization of layer IV in the somatosensory region (SI) of mouse cerebral cortex. *Brain Res* 17:205–242.
- Woolsey TA, Welker C, Schwartz RH (1975) Comparative anatomical studies of the SmI face cortex with special reference to the occurrence of 'barrels' in layer IV. *J Comp Neurol* 164:79–94.