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Organization of Area 3a in Macaque Monkeys: Contributions to the Cortical Phenotype

LEAH KRUBITZER,[1,2]* KELLY J. HUFFMAN,[1,2] ELIZABETH DISBROW,[1,3,4] AND GREGG RECANZONE[1,5]

[1]Center for Neuroscience, University of California, Davis, Davis, California
[2]Department of Psychology, University of California, Davis, Davis, California
[3]Department of Neurology, University of California, Davis, Davis, California
[4]Department of Radiology, University of California, San Francisco, San Francisco, California
[5]Section of Neurobiology, Physiology and Behavior, University of California, Davis, Davis, California

ABSTRACT

The detailed organization of somatosensory area 3a was examined in macaque monkeys using multiunit electrophysiological recording techniques. By examining topographic relationships, changes in receptive field size, and the type of stimulus that neurons responded to, functional boundaries of area 3a were determined and related to architectonic boundaries. One striking observation was that the location of area 3a varied with respect to the central sulcus. In one-half of the cases area 3a was on the rostral bank and fundus of the central sulcus and in the other half of the cases it was on the caudal bank and fundus of the central sulcus. In terms of topographic organization, we found that area 3a contains a complete representation of deep receptors and musculature of the contralateral body, and that the general organization of body part representations mirrors that of the primary somatosensory area, 3b. These results as well as results from studies of area 3a in ours and other laboratories indicate that area 3a is part of a network involved in proprioception, postural control, and the generation of coordinated movements. Further, comparative analysis of area 3a in a variety of species suggests that its construction is based, to a large extent, on the use of a particular body part rather than on innervation density. J. Comp. Neurol. 471:97–111, 2004.
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It is widely believed that humans are highly visual animals, and that our visual system is of prime importance to our survival, as well as to the sophisticated tasks required to live in the modern world. Consequently, most efforts to examine the mammalian brain have been directed towards understanding how we see. However, the construction of human environments is a clear testament to the importance of our hands and their use, or certainly to the coordinated use of the somatosensory and motor systems, as well as the visual system. Indeed, our ability to physically restructure our environment with our hands is one of the hallmarks of human evolution.

Unfortunately, our understanding of brain areas involved in the manual dexterity and bimanual integration necessary to perform these tasks is rudimentary. While a number of aspects of functional organization, neural properties, and connections have been revealed for somatosensory cortical areas that process cutaneous inputs in nonhuman primates (e.g., Merzenich et al., 1978; Carlson and

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*Correspondence to: Leah Krubitzer, Center for Neuroscience, 1544 Newton Ct., Davis, CA 95616. E-mail: lakrubitzer@ucdavis.edu

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Welt, 1980; Nelson et al., 1980; Robinson and Burton, 1980; Burton and Carlson, 1986; Carlson et al., 1986; Krubitzer et al., 1995a), relatively little is known about the organization of areas involved in proprioception, or the perception of the limbs in three-dimensional space. At least two areas of the primate neocortex, areas 3a and 2, are known to receive inputs from muscle spindles and joint receptors (e.g., Phillips et al., 1971; Schwarz et al., 1973; Heath et al., 1976; Hore et al., 1976; Pons et al., 1985; Huffman and Krubitzer, 2001a; see Jones and Porter, 1980, for review), and are hypothesized to be involved in proprioception and postural control (Tanji, 1975; Wise and Tanji, 1981; Huffman and Krubitzer, 2001a).

The field of interest in our study, area 3a, is not well understood for several reasons. First, area 3a is buried deep in the central sulcus in the macaque monkey and is difficult to access with an electrode, or injection pipette (Fig. 1). Also, neurons in area 3a are sometimes difficult to drive under particular anesthetic regimes, unlike neurons in 3b, which respond under most anesthetic conditions. Third, in terms of topography, the few studies conducted indicate that area 3a is less topographically organized than other somatosensory fields such as 3b, 1, and S2 (Krubitzer et al., 1998; Huffman and Krubitzer, 2001a). Finally, it is often difficult to isolate receptive fields for neurons in area 3a, since neurons respond to stimulation of deep receptors of the skin and muscles.

Despite the difficulties associated with examining area 3a, some inroads into understanding aspects of the connectivity and functional organization of this field have been made in New World monkeys (Akbarian et al., 1992, 1993; Guldin et al., 1992; Huffman and Krubitzer, 2001a,b). These previous studies are exciting because the results suggest the complex nature of area 3a in primates. For example, studies in marmosets indicate that neurons in area 3a respond predominantly to stimulation of deep receptors, that this field contains a complete representation of the contralateral body, and that area 3a has as many or more connections with motor cortex and posterior parietal cortical areas than with traditionally defined somatosensory areas (Darian-Smith et al., 1993; Huffman and Krubitzer, 2001b). Further, other laboratories have demonstrated that the ventral portion of area 3a in both human and nonhuman primates contains neurons that process vestibular inputs (Guldin et al., 1992; Akbarian et al., 1992; Lobel et al., 1999). These studies suggest that area 3a is part of a cortical network involved in generating instructions to move a particular body part with respect to other body parts, such as the hands with respect to the head, or the digits relative to each other. Further, areas 3a and 2 work in conjunction with other somatosensory areas, visual areas, and the motor and vestibular systems to allow specialized skin surfaces, such as multiple classes and subclasses of sensory receptors of the glabrous hand, to interface efficiently and maximally with objects in a three-dimensional physical environment.

Unfortunately, New World primates do not provide the best model for understanding the cortical mechanisms of control of the hands, which play such a critical role in complex human behavior. Marmoset monkeys have a derived hand with claws and limited manual dexterity. While arboreal squirrel monkeys are relatively dexterous, their prehensile abilities, specifically digital control and tactile discrimination, are inferior to terrestrial Old World monkeys, apes, and humans (Welles, 1976). Therefore, we explored the organization of area 3a in the Old World macaque monkey, which may serve as a better model for understanding aspects of human cortical organization involved in the use of the hand in object exploration and manipulation, reaching and grasping, and visuo-somato integration necessary for directed movements.

MATERIALS AND METHODS

Multiunit microelectrode recording techniques were used to identify the location, boundaries, and topographic organization of cortical area 3a in four adult macaque monkeys (*Macaca mulatta*). Complete maps of area 3a were generated in two cases and partial maps were made in two cases. Three cortical hemispheres were manually flattened and cut parallel to the surface and one hemisphere was cut horizontally. Flattened sections were stained for myelin (Gallyas, 1979). Horizontal sections were alternately stained for myelin and Nissl substance. Myeloarchitectonic and cytoarchitectonic boundaries were related to electrophysiological recording results. All experimental protocols were approved by the Animal Use and Care Administrative Advisory Committee of the University of California, Davis, and conformed to NIH guidelines.

Abbreviations

Body parts

ch	chin
d	digit
el, elb	elbow
fa	face
fl	forelimb
ft	foot
gen	genitals
ha	hand
hl	hindlimb
isc.call.	ischial callosities
j	jaw
ll	lower lip
mvmt	movement
p	pads
sh	shoulder
sn	snout
tr	trunk
tt	tip tongue
ul	upper lip
utr	upper trunk
vb	vibrissae
wr	wrist

Descriptive portions of body part, or location.

di or dist	distal
do	dorsal
glab	glabrous
mid	middle
pr or prox	proximal
up	upper
v	ventral

Directions

M	medial
R	rostral

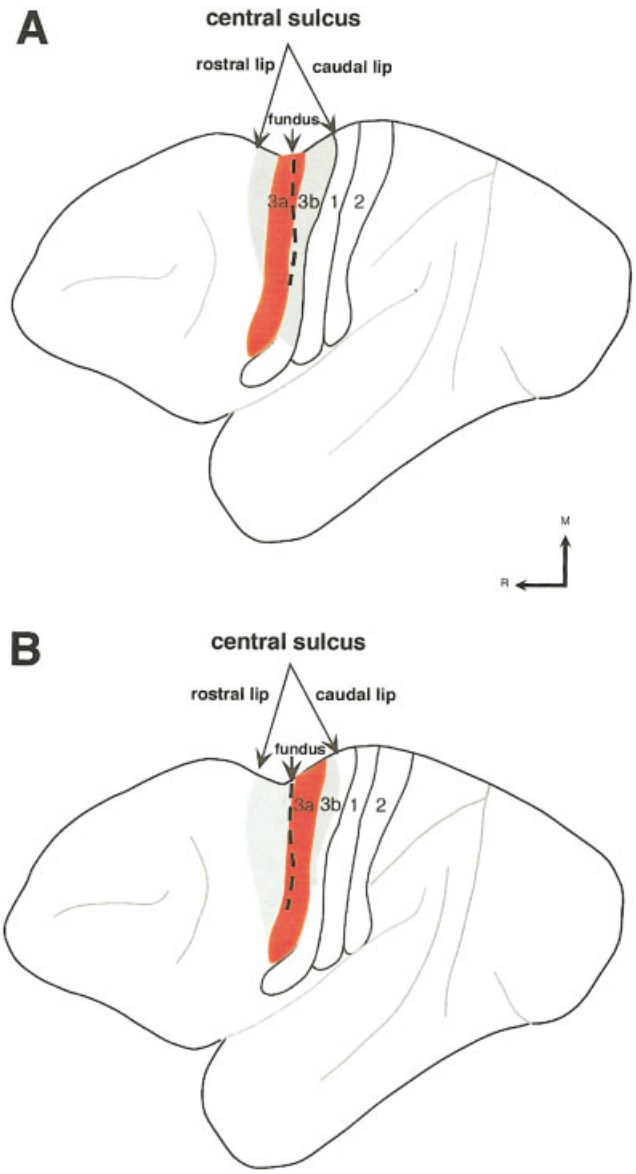

Fig. 1. Lateral views of a macaque brain (*Macaca mulatta*) with the central sulcus opened to reveal cortical areas 3a (red) and 3b buried in the sulcus. In **A**, area 3a lies on the fundus and rostral bank. In **B**, area 3a resides on the caudal bank and fundus of the central sulcus. Black lines denote architectonic boundaries, gray shading represents the banks of the central sulcus, and the dashed line represents the fundus. Thin black lines denote sulci. Medial is up and rostral is to the left.

Surgical procedures

Aseptic surgical procedures were used in all terminal electrophysiological experiments. Each animal was initially anesthetized with ketamine hydrochloride (10 mg/kg, IM). Once anesthetized, the animal was intubated and cannulated and a surgical level of anesthesia was maintained with the inhalation anesthesia, isoflurane (1.5–2% + 1 L/min O_2). Fluid levels were maintained with a continuous drip of lactated Ringer's (LS) solution alternated with LS + 2.5% dextrose (10 ml/kg/min, IV). Once anesthetized, the skin was cut, the temporal muscle retracted, and a craniotomy was performed over the anterior parietal cortex and the posterior frontal cortex, exposing both the precentral and postcentral gyri. Next, an acrylic well was built around the skull opening and filled with silicon fluid to maintain cortical temperature and to prevent desiccation. Throughout the recording experiment, heart rate, body temperature, blood oxygenation levels and fluid levels were monitored and maintained, and the animal was ventilated.

Electrophysiological recordings

A digital image of the exposed cortical surface was taken with a Pixera PVC100C digital camera (Pixera, Los Gatos, CA) so that electrode penetration sites, lesions, and probes could be related to blood vessel patterns. At the beginning of each recording session, both the rostral and caudal bank of the central sulcus was explored to determine the location of area 3a and 3b. This initial investigation was important because the position of area 3a varied greatly from animal to animal. Once the position of area 3a was determined, dense mapping commenced. The recording electrode (low-impedance tungsten-in-glass microelectrodes, 5 MΩ at 100 Hz; 30 μm tip diameter) was inserted into the cortex on either the pre- or postcentral gyrus and was advanced, using a hydraulic microdrive, down the bank of the central sulcus parallel to cortical layers. Recordings were made in layer IV in 500-μm steps along the entire mediolateral extent of the gyrus.

For each recording site, the entire body surface was stimulated with light displacement of hairs, soft brushing of the skin, light to moderate taps, limb manipulation, and pressure. Neuronal responses were amplified, displayed on an oscilloscope, and heard through a loudspeaker. Receptive fields (RFs) for neurons at each recording site were determined and drawn on pictures of the body, and stimulus preferences were noted. Receptive fields in area 3b were readily isolated since cutaneous receptors are very sensitive and easily localized. Great care was taken to precisely isolate the RFs for neurons in area 3a. For example, to isolate a receptive field on the digits, first the entire body was stimulated with brushes and fine probes to test if the recorded neurons responded to cutaneous stimulation. Then, the entire body was stimulated more intensely and the appendages were manipulated to determine if neurons responded to stimulation of deep receptors. If this procedure indicated that the receptive field was somewhere on the forelimb, for example, the shoulder was immobilized and the portion of the forelimb distal to the shoulder was stimulated with pressure or controlled joint flexion and extension. Then the elbow and the entire limb distal to the elbow was immobilized, and the shoulder was stimulated (lightly tapped, rotated, extended). The shoulder and elbow were then immobilized and the wrist and hand were stimulated; the wrist was immobilized and then the hand was stimulated; finally, four digits were immobilized and the nonimmobilized digit would be stimulated. In this way, we were able to identify with accuracy the region of the body where stimulation of muscle spindles and deep receptors in the skin occurred. Because the size of the macaque monkey is substantially larger than the marmoset, isolation of receptive fields in the macaque was somewhat easier than in marmoset monkeys (e.g., Huffman and Krubitzer, 2001a). This pro-

cedure for identifying receptive fields was done for hundreds of recording sites over a period of 2–3 days.

Throughout these experiments, electrolytic lesions (10 μA for 10 sec) were made at strategic locations in area 3a for later identification in histologically processed tissue. In one case, a probe was inserted into the cortex to mark the recording site location and electrode angle. The exact position and depth of the lesion was identified on the digital image of the exposed neocortex and was noted in the records to further aid in reconstructing electrophysiological data and histological results.

Histological processing

Upon completion of the recording experiment, the animal was transcardially perfused with 0.9% saline in 0.1 M phosphate buffer (PB), followed by 4% paraformaldehyde in PB (pH 7.4), and then 4% paraformaldehyde in 10% sucrose PB. In three cases (cases 1–3) the corpus callosum was transected and the cortex was peeled from the brainstem and diencephalon; sulci were delicately opened and the cortical gyri were flattened. The entire cerebral hemisphere was manually flattened between a lightly weighted large glass slide and a large Petri dish filled with 4% paraformaldehyde in 30% sucrose PB. In case 4, the cortical hemisphere was left intact for sectioning in the horizontal plane. For all cases, the brain was soaked overnight (12–16 hours) in 4% paraformaldehyde in 30% sucrose PB. We chose to flatten the cortex and cut it tangentially in most of our cases because accurately reconstructing electrode tracks with hundreds of recording sites in gyrencephalic brains is very difficult. Flattening the cortex allowed us to recover electrode tracks and angles with greater accuracy and to better appreciate the total extent of the field. This method of examining the cortex has proven useful in a number of studies of somatosensory cortex in primates as well as other mammals (e.g., Huffman and Krubitzer, 2001a; Krubitzer et al., 1995a; Slutsky et al., 2000).

After fixation and cryoprotection, flattened and nonflattened cortices were frozen on a sliding microtome stage. Flattened cortices were sliced parallel to the pial surface, into 60-μm sections. The cortex cut in the horizontal plane was sectioned at 50 μm. All cases were stained for myelin using the Gallyas method (1979) to reveal cortical architecture (Fig. 2). For the nonflattened hemispheres, alternate sections were mounted on glass slides and stained for Nissl substance or cytochrome oxidase reactivity (Carroll and Wong-Riley, 1984).

Data analysis

Entire electrode tracks, or portions of the tracks, were often observed in a single section in the flattened neocortex stained for myelin. Lesions and probes were identified and the depth of the recording sites were located on each track and related to myeloarchitectonic boundaries observed throughout the entire series of myelin-stained tissue. For the horizontally cut tissue, portions of electrode tracks were identified and architectonic boundaries were drawn on individual sections and a 3D reconstruction was made as described previously (Disbrow et al., 2000). Reconstructions of the sections stained for myelin, Nissl, and/or cytochrome oxidase (CO) were related to the physiological maps by matching blood vessel patterns, lesions, and electrode tracks. In all cases the entire series of sections stained was analyzed using a camera lucida attached to a light microscope.

To determine the internal organization of area 3a and its boundaries, several criteria were used. These included changes in neuronal response (e.g., good response in area 3a vs. no response in motor cortex at its rostral boundary), changes in the type of stimuli neurons responded to (cutaneous vs. deep), reversals in receptive field progression across boundaries, and architectonic distinctions. In all cases there was a very strong correlation between the area 3a–3b physiological boundary (where neuronal stimulus preference switched from deep to cutaneous) and the area 3a–3b architectonic boundary (Fig. 2). This was also true for the area 3a–M1 boundary, where neurons in area 3a responded to stimulation of deep receptors, and neurons in M1 were not responsive to any stimulation. To generate maps of area 3a, lines were interposed midway between recording sites in which neurons had receptive fields on the same body part and recording sites in which neurons had receptive fields on a different body part. If a recording site had neurons on some combination of overlapping body parts from an interposed area, a line bisected this recording site. In this way, topographic maps of area 3a were generated (Figs. 3–6).

Digital images were taken with an RT-spot camera (Diagnostic Instruments, Sterling Heights, MI). After acquisition, images were cropped and labeled using PhotoShop 7 (Adobe Systems, San Jose, CA) and Canvas 9 (ACD Systems, Saanichton, BC, Canada). Minor adjustments for brightness and contrasts were made with PhotoShop prior to assembly of the final plate.

RESULTS

Area 3a: location and functional boundaries

Electrophysiological recording techniques were used in four macaque monkeys to identify a cortical region in which neurons responded to the stimulation of deep receptors in the skin and muscle. This region, area 3a, was located between primary somatosensory cortex (area 3b) and primary motor cortex (M1), deep in the central sulcus (CS; Fig. 1). The location and rostral/caudal borders of area 3a were identified by combining cortical architecture (Fig. 2) with electrophysiological recording results (Figs. 3–6; Table 1). Unexpectedly, the position of area 3a within the central sulcus varied dramatically from animal to animal. In two cases area 3a resided on the rostral bank and fundus of the central sulcus (Figs. 3, 6) and in two cases area 3a was located on the caudal bank and fundus of the central sulcus (Figs. 4, 5). The border between areas 3a and M1 was readily identified electrophysiologically in the two cases in which area 3a was on the rostral bank of the CS because neurons in area 3a responded well to stimulation of deep receptors, while neurons in M1 did not respond to any type of somatic stimulation under our recording conditions (Figs. 3, 6). Likewise, in the two cases in which area 3a was mostly on the caudal bank of the CS, the boundary between areas 3a and 3b was readily distinguished electrophysiologically by a change in the class of receptors that neurons in each field responded to (Figs. 4, 5). Neurons in area 3b responded to stimulation of cutaneous receptors in the skin, whereas neurons in area 3a responded predominantly to stimulation of muscle spindles and deep receptors and, at a few sites, to stimulation

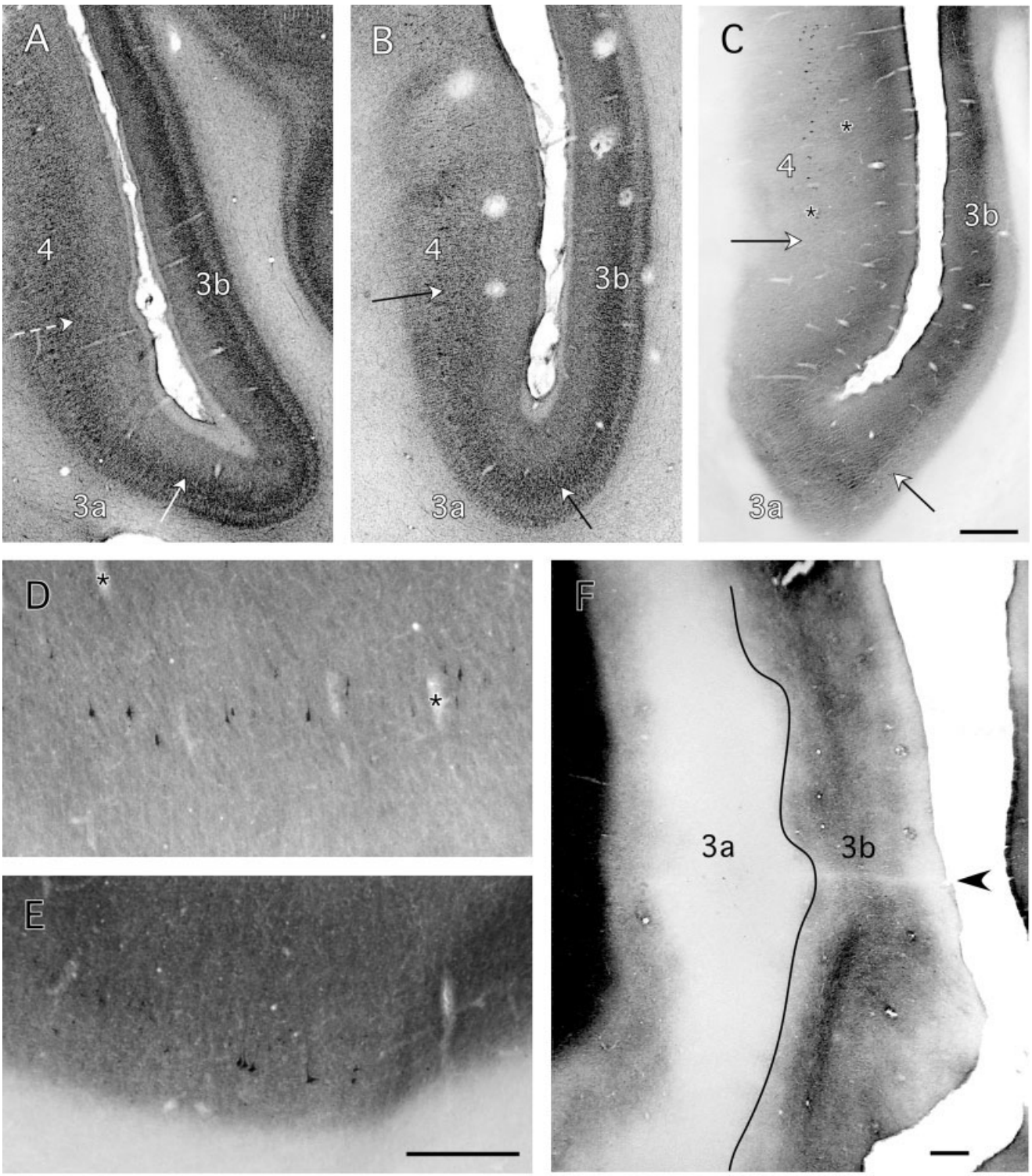

Fig. 2. **A:** Digital images of a horizontally sectioned cortex in case 99-16 (**A–E**) and tangentially sectioned cortex in case 98-30 (**F**). In A and B, cortex has been stained for Nissl substance, in C–E cortex is reacted for cytochrome oxidase, and in E, the cortex has been stained for myelin. B: In sections stained for Nissl (A,B), area 3b is distinguished by its prominent layer IV, area 4 is distinguished by an indistinct layer IV, and although not revealed with these low-power images, by large pyramidal cells in layer V (C,D). Traditionally, area 3a has been considered a transitional zone because its layer IV is not as well developed as in 3b, and although large pyramidal cells can be identified, they are sparse and less evenly distributed compared to area 4 (compare C,D,E). The image in E was taken at the fundus of the central sulcus. The presence of pyramidal cells is particularly clear in sections stained for cytochrome oxidase in both area 4 (D) and 3a (E). In cortex that has been sectioned tangentially, area 3a can be distinguished from 3b by a lack of dense myelination (F). Although flattening artifact can make portions of area 3a appear much lighter than area 3b in this section, a reconstruction through the entire series of sections allows one to draw this boundary with accuracy. The arrows in A–C and the black line in F mark architectonic boundaries. The white spots in A and B are portions of electrode penetrations from our electrophysiological mapping on both sides of the sulcus. The small arrow in F marks the hand/face boundary of area 3b as distinguished by a myelin light strip. In A,B rostral is to the right and medial is to the bottom; in D caudal is up and medial is to the right; In E rostral is to the right and medial is to the bottom; in F, rostral is left and medial is to the top. Scale bars = 1 mm.

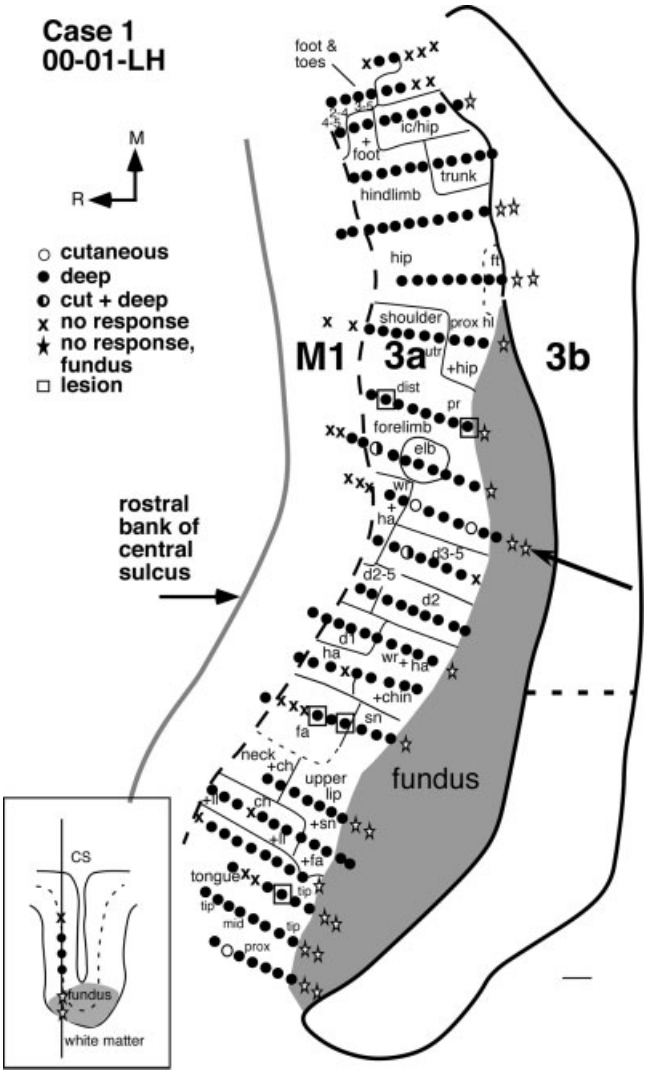

Fig. 3. A reconstruction of the topographic organization of area 3a in the left hemisphere of case 1. Electrophysiological recording results demonstrate that area 3a contains a complete representation of the deep receptors in the skin and muscles, with the toes and foot represented most medially, followed in a mediolateral progression by the hindlimb, trunk, shoulder, and forelimb, including the elbow, and wrist representation. The representation of the hand and digits is lateral to this, followed by the representation of the face (the chin, face, neck, lips, and snout, followed by the tongue). In this case, area 3a was located on the rostral bank of the central sulcus and fundus (shaded gray area). The inset is a schematic drawing of the central sulcus, electrode (straight line), recording sites, layer IV (dashed line), and fundus (shaded gray). While the topography of area 3a mirrored that of area 3b, the details of organization were less precise. In this case, only digits 1 and 2 were represented in exclusive cortical territory. All circles represent recording sites where multiunit activity was observed from somatic stimulation of the contralateral body. Thick black lines mark combined architectonic and physiological boundaries; thin black lines mark physiological distinctions between body part representations. The pale gray line represents the lip of the rostral bank of the central sulcus, and the dark gray shaded area marks the fundus of the central sulcus. A thick, black, dashed line marks the hand–face septum in area 3b, which is defined architectonically. See key for symbol designation. Abbreviations in Table 1. Medial is up, rostral is to the left.

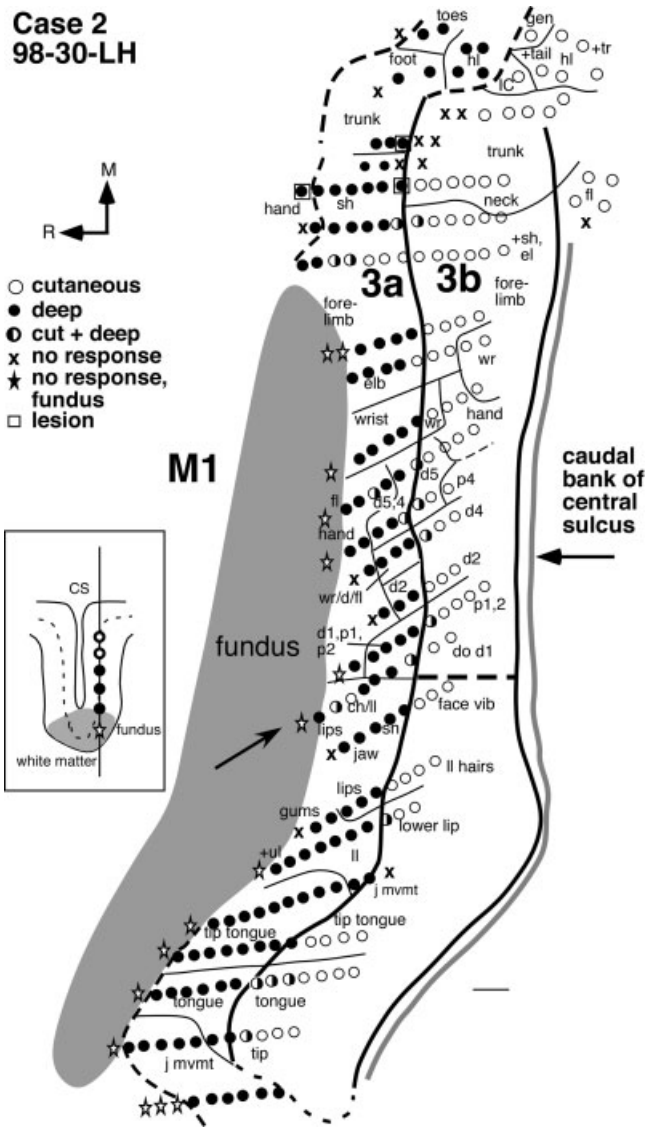

Fig. 4. A reconstruction of the topographic organization of area 3a and neighboring area 3b in the left hemisphere of case 2. In this case, most of area 3a was located on the posterior bank of the central sulcus and fundus (see inset). The overall topographic organization is like that described for the previous case, but the details of location of representation of different body parts varies across cases. The pale gray line marks the caudal bank of the central sulcus. Conventions as in previous figures. Scale bars = 1 mm.

of cutaneous receptors (Figs. 4–6). The 3a/3b boundary was also determined by observing changes in cortical architecture (Fig. 2) coincident with reversals of RFs across the boundary, re-representation of receptive fields for the different classes of receptors (deep and cutaneous), and receptive field size differences (Figs. 7–12).

Relationship between functional maps and cortical architecture

In three cases (1–3) the cortical architecture was examined in flattened cortex that was sectioned parallel to the pial surface and stained for myelin (Figs. 3–5). The entire

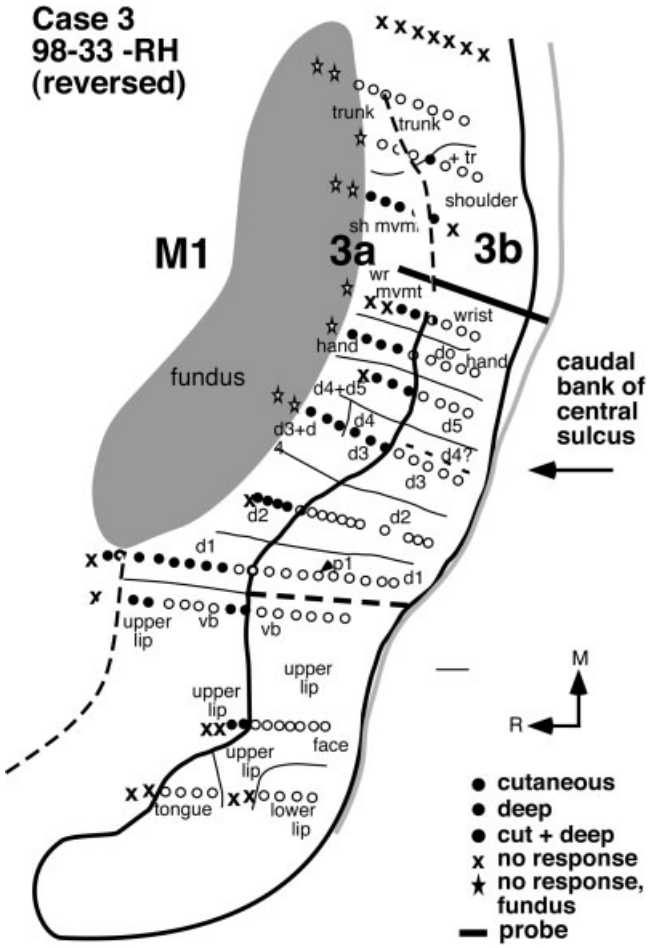

Fig. 5. A reconstruction of the topographic organization of area 3a and neighboring area 3b in the right hemisphere of case 3. In this case, most of area 3a was located on the posterior bank of the central sulcus. The overall topographic organization is like that described for the previous case, but the details of location of representation of different body parts varies across cases. This right hemisphere is presented with medial up and rostral to the left for clarity; hence, it is termed "reversed." Conventions as in previous figures. Scale bar = 1 mm.

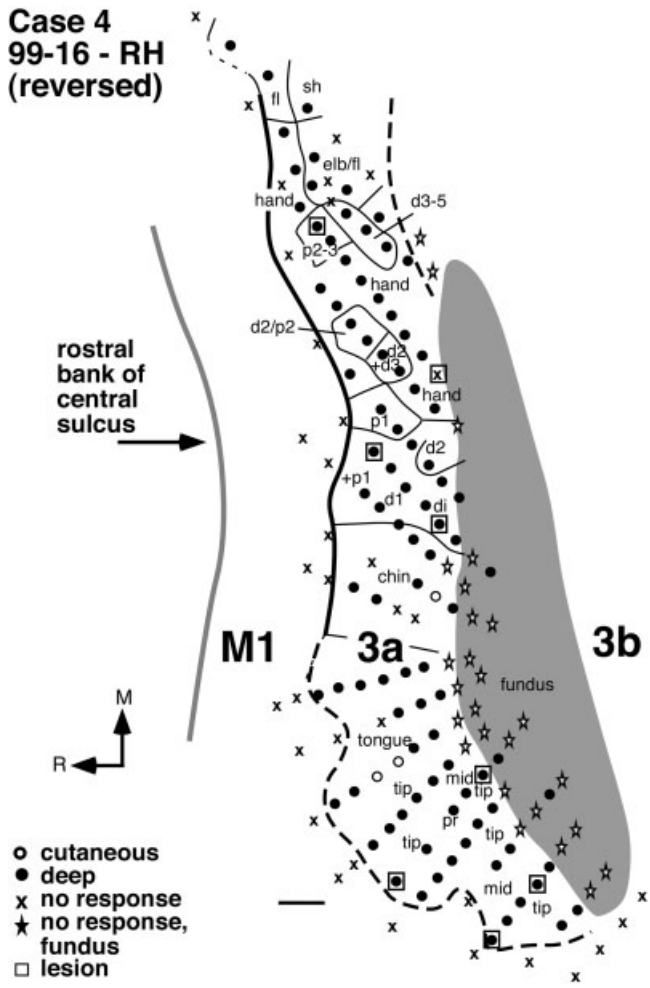

Fig. 6. A reconstruction of the topographic organization of area 3a in the right hemisphere of case 4. In this case, most of area 3a was located on the rostral bank of the central sulcus and fundus. The overall topographic organization is like that described for the previous case, but the details of location of representation of different body parts varies across cases. This right hemisphere is presented with medial up and rostral to the left for clarity; hence, it is termed "reversed." Conventions as in previous figures. Scale bar = 1 mm.

series of myelin-stained sections through the flattened cortex was reconstructed and matched with electrophysiological recording results by coregistering blood vessel patterns, electrode tracks, and lesions as landmarks. Area 3b was distinct in this preparation as a darkly myelinated area, with sharp boundaries (Fig. 2). At its caudal boundary, area 1 was distinguished from area 3b as a lightly to moderately myelinated field. Lateral to 3b, areas S2 and PV were moderately myelinated. Area 3a bordered area 3b rostrally and was distinguished by its moderate staining for myelin (Fig. 2F). When all sections in an entire series were examined, area 3a was consistently observed as a thin, lightly to moderately myelinated strip of cortex, residing between the more densely myelinated M1 (area 4) rostrally and area 3b caudally. Both the cytoarchitecture and cytochrome oxidase staining were examined in horizontally sectioned cortex in case 4. In Nissl-stained tissue (Fig. 2A,B), area 3a contained a thin, attenuated granular layer (layer IV) and a thick layer V with a scattering of large pyramidal cells. This was particularly apparent in sections stained for cytochrome oxidase (Fig. 2E). This cellular organization differs from the surrounding areas in the following ways: area 3b has a very thin layer V and a prominent layer IV, and M1 is mostly agranular with little to no layer IV cells and a very distinct layer V with large pyramidal cells (Fig. 2A,C,D). Although the match between the architecture and electrophysiological staining was often difficult to ascertain, in most cases the rostral and caudal boundaries of area 3a could be ascertained, except when they resided on the fundus.

Internal organization of area 3a and surrounding areas

Two complete maps (Figs. 3, 4) and two partial maps (Figs. 5, 6) of area 3a were generated. All maps of area 3a

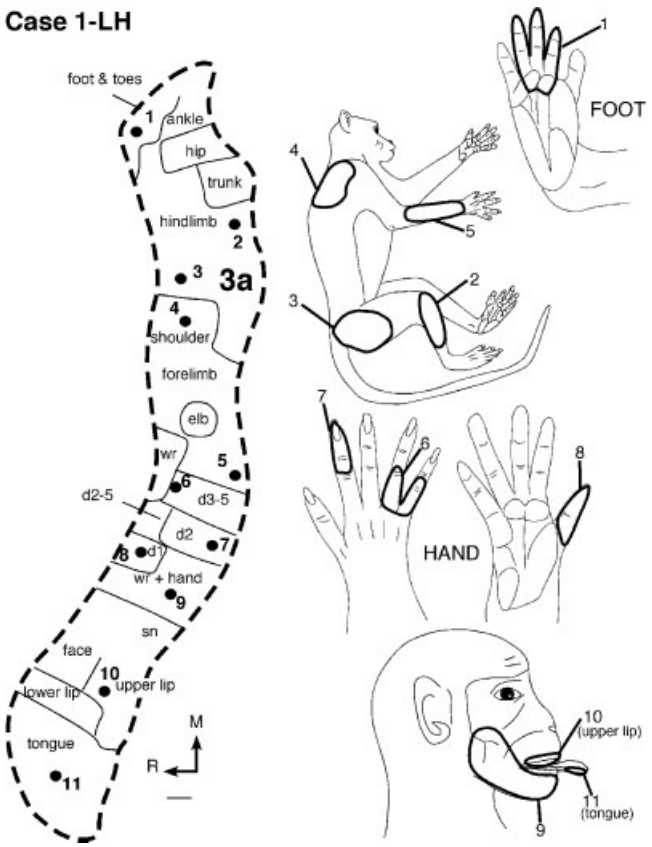

Fig. 7. A simplified reconstruction of the map of area 3a from case 1 (Fig. 3) illustrating receptive fields for neurons recorded from different mediolateral levels in area 3a. Neurons in all 11 recording sites shown had receptive fields on different body parts and demonstrate the mediolateral organization of area 3a from the toes to the tongue. Numbered sites in the map at the left correspond to numbered receptive fields for neurons at those sites drawn on the body parts to the right. Conventions as in previous figures. Scale bar = 1 mm.

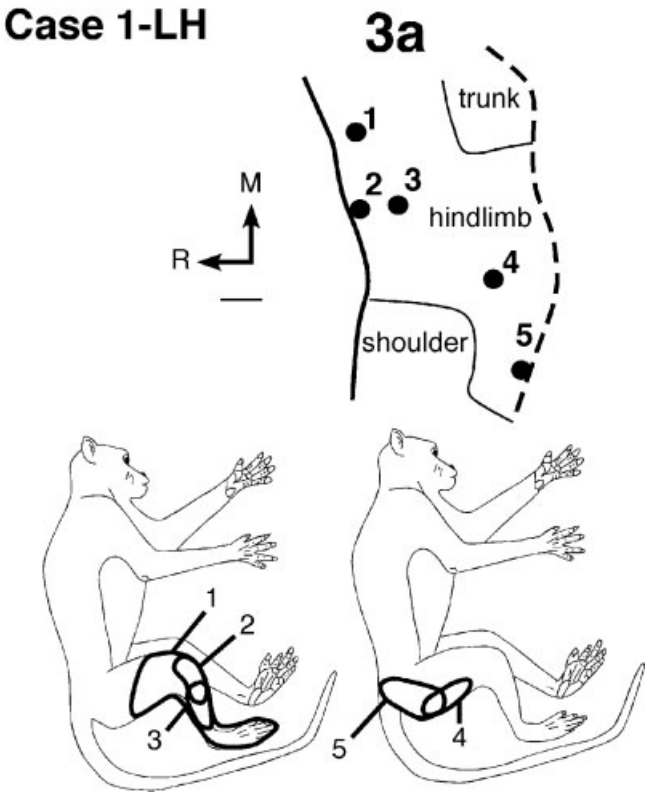

Fig. 8. Rostral to caudal receptive field (RF) progression through the hindlimb representation of area 3a in the left hemisphere of case 1. The proximal hindlimb is located rostromedially in area 3a and the distal hindlimb is represented caudolaterally in area 3a. Conventions as in previous figures. Scale bar = 1 mm.

and surrounding cortical areas were made by combining electrophysiological recording results and myeloarchitectonic or cytoarchitectonic boundaries. Area 3a was ~28–30 mm in its mediolateral extent and 3–4 mm in its rostrocaudal extent and contained a representation of the contralateral body (Figs. 3–7). Although the representations of the tail and genitals were not observed in area 3a (Figs. 3–6), this may be because they reside in cortex near the sagittal sinus, which we did not explore. Another possibility is that these body regions are not represented in area 3a of macaque monkeys. The gross topography of area 3a was like that of area 3b in that there was a mediolateral progression of body part representations, with the foot, toes, and hindlimb (including the hip and ischial callosities) represented most medially. The trunk, forelimb, hand, and digit representations were found more laterally. The representations of the chin, face, and oral structures were located most laterally in area 3a (Fig. 7).

The following results describe the details of the organization of area 3a from medial (hindlimb representation) to lateral (oral structure representation) and focus on consistencies across cases, variability within particular representations, reversals of receptive fields across the 3a/3b boundary, and receptive field size.

Representation of the hindlimb and trunk. In the two cases in which the recording density was high (Figs. 3, 4), we were able to identify the foot, toes, and hindlimb representations in the far medial location of area 3a. The overall topography was similar in both cases in that the toes were represented medial to the hindlimb. However, there was variability between cases. In case 1 (Fig. 3) the foot and toes were represented together and the ankle representation was caudal to the foot and toe representations. In case 2 (Fig. 4) the foot representation was lateral to the representation of the toes. In case 1 (Fig. 3) the hindlimb representation was lateral to the toe and foot representations, whereas in case 2 (Fig. 4) the hindlimb representation was caudal to the representations of the toes and foot. The region of 3a that represents the toes was small, and RFs for each cluster of neurons recorded typically encompassed more than one toe (Fig. 7, RF1). While the representation of the toes was not precise, there was a progression of representation from toe 1 (T1) to T5 from rostral to caudal in area 3a (Fig. 3). Unlike area 3b, in which there is a clear progression of receptive fields from dorsal to ventral, with a progression in cortex from caudal to rostral, such topographic order was not observed for the hindlimb representation in area 3a (Fig. 8). In the two cases in which the maps were comprehensive (Figs. 3, 4), the hindlimb representation abutted the trunk representation, although there was variation in the position of the

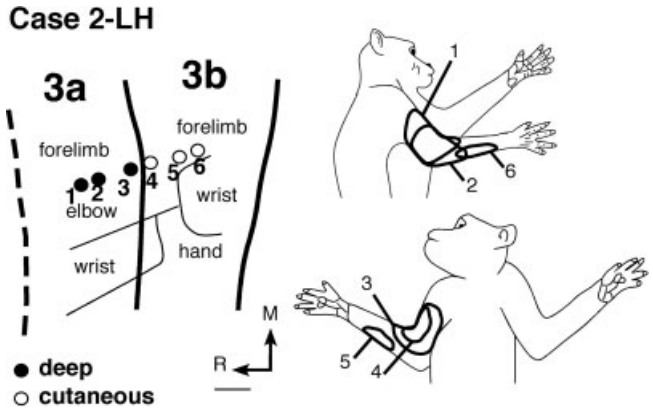

Fig. 9. Receptive field (RF) progression demonstrating an RF reversal and change in stimulus preference across the 3a/3b border. The RF progression illustrated here was through the forelimb representations in areas 3a and 3b in the left hemisphere of case 2. The RF for neurons at recording site 1 was located on the dorsal proximal forelimb; the RF for neurons at location 2 was on the dorsal proximal to middle portion of the forelimb. As the recording sites approached the 3a/3b border, RFs moved onto the ventral elbow (RF 3). As recording sites crossed the 3a/3b border, receptive fields for neurons at those sites reversed. These changes in RF progression and the type of stimulus that generated a neural response were correlated with a change in myeloarchitecture. Conventions as in previous figures. Scale bar = 1 mm.

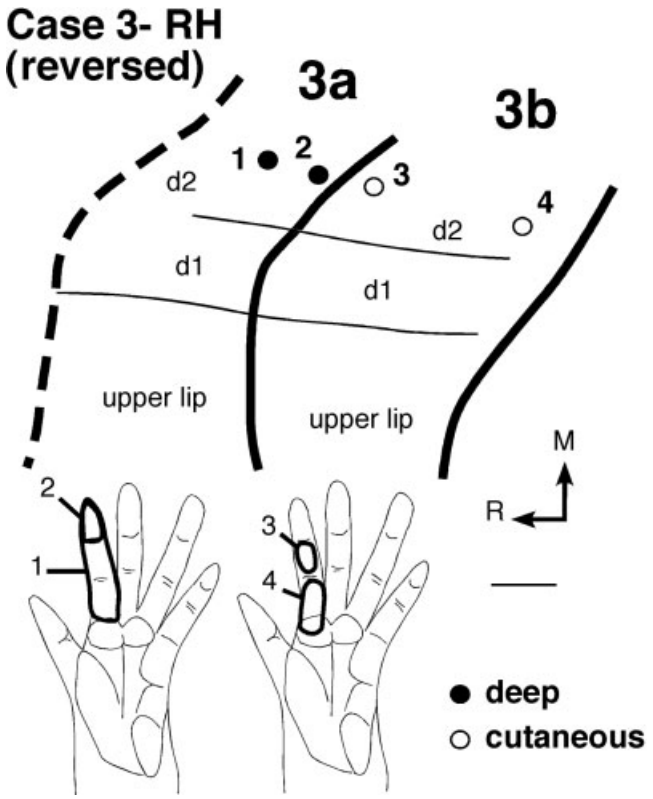

Fig. 10. RF progression demonstrating an increase in the size of receptive fields on the second digit and a change in stimulus preference of neurons in areas 3a and 3b. These electrophysiological changes were correlated with a change in myeloarchitecture. Conventions as in previous figures. Scale bar = 1 mm.

trunk representation relative to the hindlimb representation. In case 1 the trunk representation was caudal to the hindlimb representation, whereas in case 2 the trunk representation was lateral to the hindlimb representation (Figs. 3, 4). The trunk representation was small, although receptive fields could sometimes be localized to the upper vs. lower trunk.

Representation of the shoulder, forelimb, and hand. In all cases there was a progression of representation from the proximal shoulder to the elbow, wrist, and hand representation with a progression in recording sites from medial to lateral (Fig. 7 RFs 4–8). In three cases the shoulder representation was mapped in detail (Figs. 3–5) and in two of these it was observed just lateral to the trunk representation (Figs. 4, 5). In the other case, it was adjacent to the representation of the hip (Fig. 3). In two cases the shoulder representation was just medial to (and abutting) the representation of the forelimb (Figs. 3, 4), and in two cases it was medial to the representation of the wrist and hand (Figs. 5, 6). Within the forelimb representation, neurons located rostrally had receptive fields on the dorsal surface of the body (Fig. 9, RFs 1, 2). As recording sites progressed caudally, receptive fields for neurons at those sites moved onto the ventral forelimb (Fig. 9, RF 3). As recording sites crossed the 3a/3b boundary and moved caudally (towards the dorsal surface or lip of the CS), receptive fields for neurons reversed and moved from the ventral forearm to the dorsal forearm (Fig. 9, RFs 4–6). It should be noted that in many instances the amplitude of the stimulus was too high to allow us to distinguish dorsal from ventral muscle groups.

In three cases, a separate representation of the elbow was observed and in all cases it was lateral to the forelimb and shoulder representations (Figs. 3, 4, 6). Even in cases where the mapping density was high, only a small portion of area 3a was devoted strictly to the elbow representation (Figs. 3–6). A wrist or wrist and hand representation was observed in all cases lateral to the elbow or shoulder representation. As with the representation of the elbow, the amount of cortex devoted to the wrist representation alone was small. It should be noted that the elbow or the wrist representations were commonly encompassed in the large receptive fields of the forelimb (e.g., Fig. 9, RF 2, Fig. 7, RF 5).

In all cases the hand representation was lateral to the wrist representation and representations of the digits of the hand could be identified. However, the topographic organization of the hand and digits was less precise than in area 3b. The hand representation in area 3a was large and receptive fields on the hand incorporated the entire hand, including the digits, or the dorsal and ventral portions of the hand excluding the digits. In one case the pads of the hand could be distinguished as a separate representation from other parts of the hand (Fig. 6). The representation of the hand in area 3a is a marked deviation from that observed in area 3b. In area 3b, receptive fields for neurons are limited to a small portion of the hairy or glabrous surface of the hand, or are restricted to a small portion of a single digit (Fig. 10, RF 3; Fig. 11). There have never been any reports in macaque monkeys of large receptive fields for neurons in area 3b that encompass the entire glabrous and hairy hand.

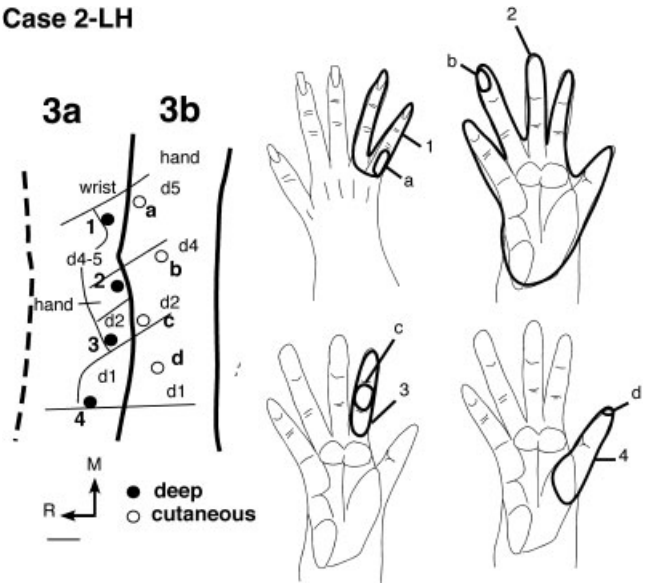

Fig. 11. RF re-representations at distantly located recording sites in areas 3a and 3b in the left hemisphere of case 2. The RF for neurons at recording location 1 in area 3a is similar, but larger than the RF for neurons at recording location a in area 3b. Additional re-representations were observed at locations 2 and b, at 3 and c, and at 4 and d. Conventions as in previous figures. Scale bar = 1 mm.

While the digit representations tended to be topographically organized from D5–D1 in a medial to lateral progression in area 3a, individual digits were not always exclusively represented in this field. For instance, in all cases (Figs. 3–6) neurons often had receptive fields on D3 and D4, D4 and D5, or D3, D4, and D5 rather than on any of these digits alone. In case 3, only three recording sites contained neurons with a receptive field limited exclusively to D3 or D4 (Fig. 5). Interestingly, in three of the four cases D1 and D2 were represented in exclusive cortical territory (Figs. 3, 5, 6), and in one case, for some of the recording sites, D1 was represented in conjunction with P1 or P2 (Fig. 4). Although RFs for neurons in area 3a were larger than those in area 3b, there was a trend for the distal portion of digits 1 and 2 to be represented at the caudal portion of the field. As recording sites progressed from rostral to caudal in area 3a, RFs for neurons at those sites progressed from the entire D2 to the distal part of D2 (e.g., Fig. 10, RFs 1, 2). As recording sites crossed the 3a/3b boundary, RFs for neurons at those sites became dramatically smaller and reversed progression from middle to proximal in area 3b. Although RFs were duplicated in areas 3b and 3a, the RFs for area 3a neurons were consistently larger (see Fig. 11, compare RFs 1 and a, 2 and b, 3 and c, 4 and d).

Representation of the face and oral structures. In all cases the representations of the face, chin, lips, jaw, and oral structures were located laterally, and in three cases abutted the representation of the digits, specifically D1 (Figs. 4–6). Although there was a good deal of variability in the topographic organization of the face, lips, and tongue in area 3a, there was a general trend across cases for the chin to be represented most medially, the lips to be represented lateral to this, and the tongue to be represented most laterally in the field. In two cases the chin representation was immediately adjacent to the D1 representation (Figs. 4, 6); in one case the chin representation abutted the representation of the wrist and hand (Fig. 3), and in one case the mapping density in this area was low and no chin representation was observed (Fig. 5). In two cases the chin representation was bordered laterally by the representation of the face and snout (Figs. 3, 4). In the case in which the mapping density was low, only the upper lip representation was identified lateral to the representation of D1 (Fig. 5). In cases 1 and 2, the snout and face representations were bordered laterally by the representation of the lips (Fig. 3) or by the upper jaw and lips (Fig. 4). Receptive fields for neurons which represented the lips were consistently larger in area 3a than in area 3b (Fig. 12). For neurons in area 3a, receptive fields generally encompassed the entire upper and/or lower lip and portions of the adjacent face, while receptive fields for neurons in 3b were much smaller and included only a small portion of the upper or lower lip. In all cases in which the mapping density was high in this region, the tongue representation was observed laterally in area 3a (Figs. 3, 4, 6). While the proximal and distal portion of the tongue representation could be distinguished within this field, there appeared to be no topographic order in this representation. In one case, the jaw was represented at the most lateral portion of area 3a (Fig. 4).

Although our mapping density was high in two cases (Figs. 3, 4), we did not identify representations of the face area above the lips. It may be that the representations of these body parts are small, and that we simply did not have recording sites in these regions. Another possibility is that there are no representations of these body parts, since none of these structures participate in behaviorally relevant, coordinated movements except for the eyes.

DISCUSSION

In the present investigation, we demonstrate several distinctive features of organization of area 3a in macaque monkeys. First, while area 3a contains a complete representation of deep receptors of the contralateral body, the topographic organization of area 3a is not as precise as that of area 3b. Area 3a differs from area 3b in that most individual body parts are not represented in exclusive cortical territory. The second, related finding is that receptive fields for neurons in area 3a are larger than those in area 3b. The third observation is that the location of area 3a varied between animals. In half of the cases it was on the caudal bank and fundus of the central sulcus, and in half of the cases it was on the rostral bank and fundus of the central sulcus. The final observation is that the forelimb, hand, and digit representations in area 3a have a large cortical magnification factor. In the following discussion, we compare our results with those of previous studies in which area 3a has been electrophysiologically explored. We discuss the implications of our findings for interpreting anatomical, physiological, and functional imaging studies when the location of cortical fields is based on gyral and sulcal patterns. Finally, we speculate on the factors that contribute to the emergence of particular cortical fields in development and evolution.

Area 3a in primates

Area 3 was originally described in humans and other primates as a single field with a dense koniocellular layer

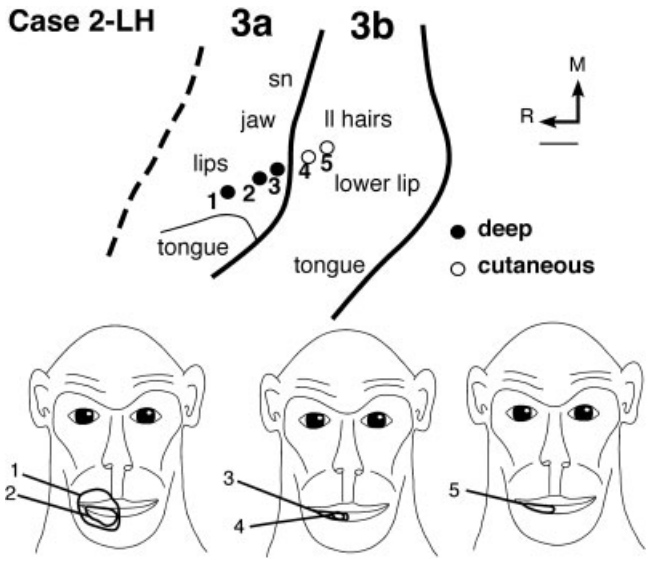

Fig. 12. Recording site progression demonstrating a change in the RF size and stimulus preference in areas 3a and 3b. The RF for neurons at recording location 1 in area 3a was located on the contralateral upper and lower lips and the area surrounding the mouth; the RF for neurons at location 2 was on the lower lip and the area below the lower lip. As the recording sites approached the 3a/3b border, RFs moved onto the medial portion of the lower lip (RF 3). In area 3b, RFs for neurons became smaller and the stimulus required to elicit a response changed from deep to cutaneous. These electrophysiologically defined differences are correlated with a change in myeloarchitecture. Conventions as in previous figures. Scale bar = 1 mm.

(layer IV) that spanned the central sulcus (Brodmann, 1909). Although Brodmann noted a transition zone between areas 3 and 4, area 3 was subdivided into two distinct architectonic areas, 3a and 3b, by Vogt and Vogt (1919). A rostral region, termed area 3a, contained a reduced granular cell layer (layer IV), and an expanded layer V with large, moderately packed pyramidal cells. The caudal region, termed area 3b, contained a densely packed granular cell layer and was subsequently demonstrated to be coextensive with the functional subdivision termed the primary somatosensory area (S1; Woolsey and Fairman, 1946; Woolsey, 1958; see Kaas, 1983, for further discussion of the history of area 3b). Although areas 3a and 3b have been considered separate cortical fields for almost a century, we have only a limited understanding of the functional properties of neurons in area 3a and its anatomical connections. Further, it is not clear whether area 3a is a purely primate phenomenon, or whether it exists in nonprimate mammals as well.

Electrophysiological, single unit recording studies in area 3a of anthropoid apes and Old World monkeys indicate that neurons respond to stimulation of deep receptors in the muscles and joints, and ultimately receive inputs from type Ia afferent pathways (Phillips et al., 1971; Schwarz et al., 1973; Yumiya et al, 1974; Heath et al., 1976; Hore et al., 1976; see Tanji and Wise, 1981, for review). Single unit studies in awake monkeys indicate that neurons in area 3a increase activity with maintained limb position (i.e., in the absence of changes in muscle length) and that neural activity reflects the velocity of movement towards a limb position, as well as the ultimate position of the limb (Tanji, 1976; Wise and Tanji, 1981). The complete topographic organization of area 3a in primates has only been described for marmosets (Huffman and Krubitzer, 2001a). This previous study demonstrated that, like area 3b, area 3a contained a representation of deep receptors and musculature of the contralateral body, although the topographic organization was less precise than in area 3b (see below for further discussion). Studies of connections of area 3a in Old World (Jones et al., 1979; Darian-Smith et al., 1990) and New World (Akabarian et al., 1992; Huffman et al., 2001b) monkeys indicate that area 3a receives input from both somatic nuclei and vestibular nuclei (Lang et al., 1979) of the thalamus such as the ventral posterior superior nucleus (VPS, VPLc of Jones et al., 1979; Darian-Smith and Darian-Smith, 1993) and the anterior pulvinar (Pla), as well as nuclei associated with the motor system such as the ventral lateral, ventral anterior, and central lateral nucleus of the thalamus.

Cortical connections of electrophysiologically defined locations in area 3a have only been described in the marmoset monkey (Huffman and Krubitzer, 2001a). The surprising result from this previous study is that area 3a has much denser connections with motor and posterior parietal areas of the neocortex than with traditionally defined somatosensory areas. Further, the distribution of connections appears to be dependent on the body part representation for which connections were determined. The forelimb representation in area 3a has very broad, topographically mismatched connections with the forelimb representation in other fields, as well as other body part representations (such as the face representation), while the foot representation in area 3a has topographically matched connections mainly with the foot representation in other cortical areas. Taken together, the data indicate that, at least in primates, area 3a appears to be involved in integrating somatic and vestibular inputs with the motor system, maintaining posture and limb position, and regulating velocity of limb movement.

Variable characteristics of area 3a: Problems with determining cortical fields from sulcal patterns

One of the more striking features of the current data is the location of area 3a in macaque monkeys with respect to the central sulcus. In two of our cases area 3a was on the rostral bank of the central sulcus and continued onto the fundus of the CS, and in two cases area 3a was on the caudal bank of the central sulcus and continued onto the fundus. The observation that the location of a cortical field can vary with respect to the sulcus has several implications for interpreting results from other functional and anatomical studies. Probably the most important implication is that cortical field boundaries cannot be reliably approximated from sulcal patterns. Thus, when examining patterns of connectivity of cortical fields, placing injections of anatomical tracers relative to sulcal patterns is obviously problematic. Another important implication relates to the interpretation of modern functional imaging studies in humans. Patterns of activation in any particular study are related to sulcal patterns, which in turn are related to cortical fields. For example, in studies of somatosensory cortical areas in the central sulcus, patterns of activation that result from somatic stimulation are pro-

posed to be in the primary somatosensory area if on the caudal bank, and area 3a if in the fundus (e.g., Moore et al., 2000). However, our work and imaging work in humans (Roland and Zilles 1994, 1998) demonstrate that cortical field location can vary dramatically with respect to the sulcal anatomy.

A final implication regards current theories about the evolution of sulcal pattern formation. One theory proposed by Welker (1990) suggests that gyri are separate structural and functional entities, much like nuclei in the thalamus, while a more recent hypothesis proposed by Van Essen (1997) suggests that tension-based morphogenesis and underlying patterns of connectivity between cortical areas account for the pattern of gyri in any particular brain. Both theories are based on the assumption that cortical field location is static with respect to sulci and gyri. Further, connectivity of cortical fields does not vary to the same degree as cortical field location relative to sulcal patterns. Thus, current hypotheses regarding the issue of gyral evolution need to be reevaluated.

Area 3a in other mammals

Studies in other mammals have identified a region of cortex just rostral to area 3b (S1) in which neurons respond to stimulation of deep receptors, although very few attempts have been made to reconcile these areas (termed differently by different investigators) with those in primates. In carnivores, such as cats (Landgren and Silfvenius (1969), raccoons (kinesthetic cortex, KC, Johnson et al., 1982), and ferrets (Leclerc et al., 1993; Hunt et al., 2000) a region just rostral to area 3b contains a number of characteristics of area 3a in monkeys, such as neural response to stimulation of deep receptors, architectonic appearance, and gross, topographic organization. Further, in other mammals, such as marsupials (see Huffman et al., 1999), rodents (see Slutsky et al., 2000, for review), insectivores (Krubitzer et al., 1997), and monotremes (Krubitzer et al., 1995b), these features are observed in a field just rostral to S1, termed R (Krubitzer et al., 1995b; Krubitzer and Kaas, 1988). Despite these similarities, the issue of whether field R is homologous to area 3a in primates is contentious. At the time this field was described in other mammals, very little information regarding the detailed organization of area 3a was available, even in primates. However, the accumulation of electrophysiological recording data in the variety of species listed above, and recent studies in primates including marmosets (Huffman and Krubitzer, 2001a) and macaque monkeys (present investigation) allows us to make more accurate inferences about the evolution of this field. It appears that all mammals have a cortical field located just rostral to area 3b (Fig. 13) which can be distinguished from motor cortex (area 4) based on a number of criteria, including functional organization, neural stimulus preference, architectonic distinctiveness, and, when available, studies of cortical and subcortical connectivity. The most parsimonious interpretation of these data is that all mammals have an area 3a that was inherited from a common ancestor. However, there are several features of organization of area 3a that have been modified in different lineages over time which appear to be related to use of behaviorally relevant body parts.

Contributions to the cortical phenotype of area 3a.

The significance of the organization we observed for area 3a in the macaque monkey is not truly appreciated until this organization is compared with that of area 3b in the same species and with area 3a in other species. For instance, when the topographic organization of area 3a is compared with that of area 3b in macaque monkeys, area 3b is observed to be more topographically precise and the cortical magnification of particular body parts, to a large extent, correlates with innervation density (Lee and Woolsey, 1975; Catania and Kaas, 1997), similar to the preferential representation of the fovea in the primary visual area (Azzopardi and Cowey, 1993). This is particularly true for representations of the digits in primates in which every digit is represented in an exclusive cortical zone. This observation is not specific to macaque monkeys, but has been observed in every primate examined regardless of the use of the hand or whether the primate in question has an opposable thumb (e.g., Merzenich et al., 1978; Carlson and Welt, 1980; Nelson et al., 1980; Sur et al., 1980, 1982; Carlson et al., 1986; Fig. 13).

In contrast, area 3a is organized quite differently in different primates. For instance, in marmosets, little if any cortical territory is devoted to the exclusive representation of any one digit. In the macaque monkey, we observed exclusive cortical territory primarily devoted to the representation of D1 and D2 in area 3a. Studies of hand use in New World monkeys indicate that most utilize a power grip to grasp objects by curling digits 2–4 toward the palm of the hand (Welles, 1976). The thumb is generally not employed in their grasping behavior. Macaque monkeys, on the other hand, are highly skilled "graspers" who employ two general techniques. The first, most common technique is to oppose D1 to D2 (precision grip), and the second technique is a power grip (Welles, 1976; Roy et al., 2000).

These observations are consistent with the hypothesis that the organization of area 3a emerges in development as a result of the actual use of the hand, while area 3b emerges predominantly as a consequence of innervation density. This hypothesis is supported by three lines of evidence. First, studies in early postnatal primates demonstrate that only area 3b is functionally and anatomically distinct on the day of birth in both New and Old World monkeys (Krubitzer and Kaas, 1998). Cortex that would normally be occupied by areas 3a, 1, and 2 contain neurons that are unresponsive to any type of sensory stimulation. Second, studies of the organization of area 3a in a variety of other species who use the hand quite differently than primates, or use the hand very little, if at all, for making tactile discriminations show a striking difference in the organization of area 3a (Fig. 13). For example, the flying fox has a highly derived hand in which the digits have evolved membranes that span between them. This digit/membrane configuration functions as a whole unit, the wing, which is adapted for flight. The flying fox has no cortical territory in area 3a that exclusively represents any digit, or even groups of digits, although such exclusive representation is present in area 3b in these mammals. Another interesting example is the marsupial striped possum. This animal has a highly derived digit 4 that it uses almost exclusively to capture insects (Van Dyck, 1983). While exclusive cortical territory for all of the digits is

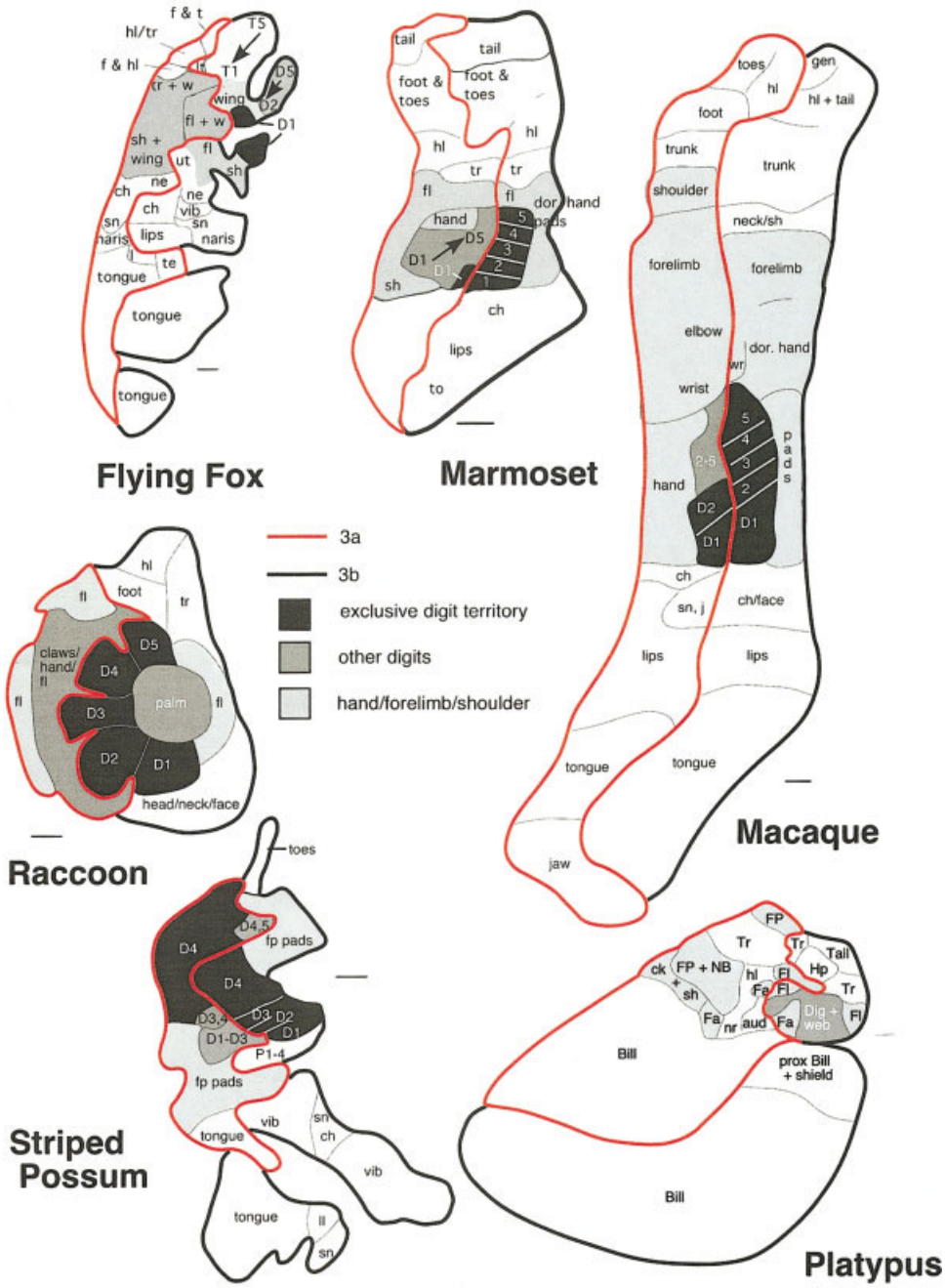

Fig. 13. The organization of areas 3a and 3b in different species of mammals. Comparative studies suggest that area 3a is common to most or all mammals examined and is likely to be homologous. Area 3a's functional organization or connections may have changed over time to produce or accommodate increasing levels of somatosensory and motor complexity. Recently, a field immediately rostral to area 3b or S1 (area outlined in red) has been described in a variety of mammals, including prototherians such as the duck-billed platypus (Krubitzer et al., 1995b), metatherians such as the striped possum (Huffman et al., 1999), and eutherians such as the flying fox (Krubitzer et al., 1998), raccoon (Johnson et al., 1982), marmoset (Huffman and Krubitzer, 2001a), and macaque monkey (current study). In all mammals, area 3a is a moderately myelinated field in which the representation of deep receptors of the skin and muscles appears to reflect species-specific behavioral specializations, rather than innervation density of a particular body part (as in 3b). This is particularly apparent when comparing the topographic representation of areas 3a and 3b within a species, and when comparing the topographic organization of area 3a across species. For example, the platypus does not use any of its digits for tactile discrimination or exploration, but uses the entire webbed forepaw for aquatic locomotion and digging. The flying fox uses only D1 for exploration. This digit is relatively free from the rest of the digits (which are adapted for flight and form the wing). Area 3b in the flying fox contains a separate representation of D1 only, and in area 3a the entire wing, including the digits, digit membranes, forelimb, and associated wing membranes are represented together, possibly as an adaptation for flight. The striped possum uses digit 4 very specifically for extracting insects from holes in the bark of trees, while the raccoon uses its entire hand, splayed across the surface of water, to capture fish. As described in the text, marmoset monkeys and macaque monkeys use their digits differently for grasping objects. The organization of area 3a in each of these species reflects these behavioral differences. Red lines denote area 3a boundaries, black lines denote area 3b boundaries, and black shading represents exclusive digit representations, dark gray shading represents other digit, or multidigit representations, and pale gray shading represents the hand/forelimb/shoulder representations. Conventions as in previous figures.

observed in area 3b (with a magnification of D4), only D4 is represented exclusively in area 3a (Huffman et al., 1999).

Finally, studies of plasticity in motor and somatosensory cortex of adult mammals using a variety of different manipulations (e.g., Jenkins et al., 1990; Recanzone et al., 1992a,b; Wang et al., 1995; Nudo et al., 1996; Classen et al., 1998; Plautz et al., 2000) demonstrate robust changes in both topography of areas 3b and 3a and the submodality of stimulation needed to elicit a response (Recanzone et al., 1992b). In most instances the cortical zone of reorganization was greater in area 3a than in area 3b in the same animal. One interpretation of these adult cortical plasticity studies is that cortical representations reflect use-dependent processes for that individual. Thus, individual variability in the topographic organization of the representation, such as that observed in area 3a of this study, is likely due to differences in the use of different body parts by each particular animal.

The three lines of data described above indicate that the construction of area 3a during development and in evolution is the result of an interaction between the motor system and the somatosensory system. This finding suggests that greater variability in cortical organization may exist for fields such as area 3a within a particular species, especially if the use of the hand is highly variable in different environments. We believe that such differences within a species exist not only for area 3a, but for a number of higher-order cortical areas. These differences in the organization of cortical fields within a species would be magnified for homologous cortical fields across species because the environmental conditions and the use of a particular body part would be dramatically different.

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