

The Organization and Connections of Anterior and Posterior Parietal Cortex in Titi Monkeys: Do New World Monkeys Have an Area 2?

Jeffrey Padberg¹, Elizabeth Disbrow^{1,2,3} and Leah Krubitzer^{1,4}

¹Center for Neuroscience, University of California, Davis, CA, USA, ²Department of Neurology, University of California, Davis, CA, USA, ³Department of Radiology, University of California, San Francisco, CA, USA and ⁴Department of Psychology, University of California, Davis, CA, USA

We used multiunit electrophysiological recording techniques to examine the topographic organization of somatosensory area 3b and cortex posterior to area 3b, including area 1 and the presumptive area 5, in the New World titi monkey, *Callicebus moloch*. We also examined the ipsilateral and contralateral connections of these fields, as well as those in a region of cortex that appeared to be similar to both area 7b and the anterior intraparietal area (7b/AIP) described in macaque monkeys. All data were combined with architectonic analysis to generate comprehensive reconstructions. These studies led to several observations. First, area 1 in titi monkeys is not as precisely organized in terms of topographic order and receptive field size as is area 1 in macaque monkeys and a few New World monkeys. Second, cortex caudal to area 1 in titi monkeys is dominated by the representation of the hand and forelimb, and contains neurons that are often responsive to visual stimulation as well as somatic stimulation. This organization is more like area 5 described in macaque monkeys than like area 2. Third, ipsilateral and contralateral cortical connections become more broadly distributed away from area 3b towards the posterior parietal cortex. Specifically, area 3b has a relatively restricted pattern of connectivity with adjacent somatosensory fields 3a, 1, S2 and PV; area 1 has more broadly distributed connections than area 3b; and the presumptive areas 5 and 7b/AIP have highly diverse connections, including connections with motor and premotor cortex, extrastriate visual areas, auditory areas and somatosensory areas of the lateral sulcus. Fourth, the hand representation of the presumptive area 5 has dense callosal connections. Our results, together with previous studies in other primates, suggest that anterior parietal cortex has expanded in some primate lineages, perhaps in relation to manual abilities, and that the region of cortex we term area 5 is involved in integrating somatic inputs with the motor system and across hemispheres. Such connections could form the substrate for intentional reaching, grasping and intermanual transfer of information necessary for bilateral coordination of the hands.

Keywords: cortical connections, functional organization, somatosensory cortex, visual cortex

Introduction

Sophisticated hand use is one of the hallmarks of primate evolution, and different groups of primates have varying degrees of manual abilities. While the morphology of the hand varies across primates from the clawed digits of marmosets and tamarins, used for scaling trees, to the glabrous hand with opposable thumbs of anthropoid primates, better suited for the manipulation and tactile exploration of objects (see Napier, 1960, 1962), most would agree that these morphological differences alone cannot explain the extreme variations in

manual behaviors across primates. Rather, changes in brain organization, particularly the neocortex, are likely to contribute to the differences in manual behaviors exhibited by different primates. In the present study, we extensively explored cortex caudal to area 3b in the New World titi monkey (*Callicebus moloch*) using electrophysiological and neuroanatomical techniques, in an effort to accurately subdivide both anterior and posterior parietal areas of the neocortex. These regions of cortex are involved in tactile discriminations, proprioception, and intramanual and bimanual abilities (reviewed by Gardner, 1988; Kalaska *et al.*, 1997; Iwamura, 2000; Wise *et al.*, 1997; Andersen and Buneo, 2002; Krubitzer and Disbrow, 2004). We then compared these results with those previously described in New World and Old World monkeys with variable manual abilities, with the goal of identifying potential cortical changes that may have occurred in conjunction with modifications in hand use across different lineages.

Comparative studies suggest that early stages of sensory processing may have been modified in different primates in relation to hand use. For example, although the presence of an area 3b has been well documented using electrophysiological recording techniques and neuroimaging techniques across all groups of primates (Nelson *et al.*, 1980; Sur *et al.*, 1980; Felleman *et al.*, 1983; Carlson *et al.*, 1986; Fox *et al.*, 1987; Krubitzer and Kaas, 1990b; Chen *et al.*, 2001; Shoham and Grinvald, 2001), the presence of other anterior parietal fields, such as area 2, is less well supported by current electrophysiological recording data. Indeed, area 2 has not been electrophysiologically identified in any non-human primate other than the macaque monkey (Pons *et al.*, 1985). Further, while area 1 has been described in squirrel, owl, cebus and macaque monkeys (Merzenich *et al.*, 1978; Nelson *et al.*, 1980; Sur *et al.*, 1982; Felleman *et al.*, 1983), it has not been identified in marmosets, tamarins or prosimian galagos, although cortex in the location of area 1 has been explored in these primates. Thus, existing data on the organization of cortex caudal to area 3b are limited in some groups of primates, and the data that do exist indicate that the organization of this cortex may vary greatly across primates.

Traditional views hold that regions of posterior parietal cortex are involved in generating complex manual abilities, and that this region of cortex has also been greatly modified in primates. Indeed, there is accumulating evidence in macaque monkeys for the role of posterior parietal area 5 in a number of aspects of manual behaviors. Single-unit studies in awake, behaving macaque monkeys indicate that area 5 is involved in programming the intention of movement (Burbaud *et al.*, 1991; Snyder *et al.*, 1997; Debowy *et al.*, 2001), in pre-shaping the hand before grasping an object (e.g. Debowy *et al.*, 2001), and

that area 5 generates body- or shoulder-centered coordinates for reaching (Ferraina and Bianchi, 1994; Lacquaniti *et al.*, 1995; see Wise *et al.*, 1997, for review). Recent work also indicates that area 5 may play a critical role in generating an internal frame of reference, necessary for the abilities described above (Iriki *et al.*, 1996, 2001; Graziano *et al.*, 2000). While the role of area 5 in generating these behaviors in macaque monkeys is beginning to emerge, it is not known whether New World monkeys possess an area 5 as defined electrophysiologically, and if they do possess an area 5, how it is organized and interconnected.

In the current investigation we used electrophysiological and neuroanatomical techniques to examine the organization and connections of cortex immediately caudal to area 3b in New World titi monkeys to determine if these animals possess an area 1, like other New World monkeys, and an area 2, like macaque monkeys. We also surveyed cortex in the location of area 5 to determine if New World monkeys possess an area 5 and if so, whether features of organization are similar to those in macaque monkey area 5.

The titi monkey is ideal for exploring these issues for two reasons. The first has to do with their manual abilities. While these animals use the hand for object exploration, manipulation and locomotion, they do not possess an opposable thumb, and their repertoire of grips and hand configurations varies markedly from that of Old World macaque monkeys, anthropoid apes and humans (Hill, 1966; Welles, 1976). Examining the organization of anterior parietal cortex in a relatively simple primate brain with less sophisticated manual abilities compared to macaque monkeys might provide insight into the evolution of cortical fields associated with hand use in primates. The second reason we chose to examine titi monkeys is that they afford the technical advantage of a smaller neocortex that is nearly lissencephalic. Thus, if these animals do indeed possess an area 5, it should reside either on the cortical surface, or on the upper bank of a very shallow intraparietal sulcus (IPS), rather than being buried in the depth of the IPS as in macaque monkeys. This configuration makes electrophysiological recordings and studies of connections easier to execute and interpret.

Materials and Methods

The organization of anterior parietal areas 3b and 1 and cortex caudal to area 1 were explored in seven titi monkeys (*Callicebus moloch*) using standard multiunit electrophysiological recording techniques, combined with architectonic analysis (Table 1). Neuroanatomical tracing studies were done in four of these animals to examine the connections of cortical areas 3b, 1, cortex caudal to area 1, and 7b/AIP (Table 2). In all cases, after an appropriate time elapsed to allow for transport of tracers, cortical areas were mapped to verify the tracer injection sites and to explore adjacent regions of cortex. All data sets were combined on a comprehensive reconstruction that included electrophysiological recording results, architectonic boundaries and cortical connections. Experimental protocols were approved by the Animal Use and Care Administrative Advisory Committee of the University of California, Davis and conformed to NIH guidelines.

Injections of Anatomical Tracers

Ten injections of anatomical tracers were made in four animals (Table 2). Animals were initially anesthetized with either telazol (10 mg/kg) or ketamine hydrochloride (10 mg/kg), and then intubated and cannulated. Surgical levels of anesthesia were maintained with the inhalation anesthetic, isoflurane (1–3%). The animals were artificially ventilated throughout the experiment. A continuous infusion of lactated Ringer's solution (6 ml/kg/h) was given intravenously, and throughout the experiment the animal's heart rate, respiration rate, temperature and

Table 1

Legend?

Case no.	Plane of section	Thickness (μm)	Tracer injection	Electrophysiological recording	
01-53	tangential	40	–	+	
01-79	tangential	40	+	+	
02-12	tangential	40	+	+	
02-18	tangential	40	+	+	
02-52	tangential	40	+	+	
03-98	tangential	30	–	+	
03-113	horizontal	60	–	+	
03-116	horizontal	60	–	–	histology
04-122	oblique	35	–	–	histology

Table 2

Tracers injected

Case no.	Site	Amount/tracer
01-79	5?	0.4 μl FE
	1	0.5 μl FR
02-12	AIP	0.3 μl BDA
	3b	0.4 μl FE
	1	0.3 μl FR
02-18	5?	0.4 μl FE
	AIP	0.4 μl BDA
02-52	5?	0.3 μl FE
	3b	0.4 μl BDA
	1	0.3 μl FR

expired pCO_2 levels were monitored and maintained. Once anesthetized and stabilized, the skin was cut, the temporalis muscle was retracted and a craniotomy was made over the posterior parietal cortex. The dura was cut and the dura flaps were gently pulled away from the opening. The intraparietal (IPS) and lateral sulci (LS) were visualized, and the location of the hand representations 3b, 1, cortex caudal to area 1 and 7b/AIP were approximated from previous maps made in titi monkeys. All injection sites were later verified using electrophysiological recording techniques (see below). Injections were made with a calibrated Hamilton syringe that was lowered into the cortex using a stereotaxically guided micromanipulator. Injections of 0.3–0.4 μl of the fluorescent tracers FluoroEmerald (7% FE; Molecular Probes, Eugene, OR) and FluoroRuby (FR; 7%, Molecular Probes), or biotinylated dextran amine (BDA; 10%) were made into areas 3b, 1, cortex caudal to area 1, and 7b/AIP in the left hemisphere (see Table 2). After the injections were complete, the brain was covered with a sterile contact lens, the dura flaps were placed over the lens, gel foam was placed over the dura flaps and either the skull was replaced and held in place with acrylic, or a new skull was made from acrylic. The temporalis muscle was sutured in place, and the skin was sutured. A recovery period of 6–12 days followed, to allow for transport of the neuroanatomical tracers prior to beginning acute electrophysiological recordings.

Electrophysiological Recording Experiments

Electrophysiological recordings were made in seven animals, four of which also received injections of anatomical tracers prior to extensive electrophysiological mapping. The anesthetic regime and surgical procedures for the acute electrophysiological recording experiments were the same as those described above with a few exceptions. First, instead of intubating the animal, a tracheotomy was performed. Second, the animals were given both dexamethasone (30 mg/kg, i.m.), and atropine (0.1 mg/kg, i.m.) at the beginning of the experiment. Finally, ~0.1 ml of 2% lidocaine hydrochloride was placed into the ear canals prior to insertion of the ear bars. Heart rate, respiration rate and body temperature were monitored continuously throughout the surgery.

Once the animal was anesthetized and stabilized, silicone fluid was placed on the exposed cortex to protect the brain from desiccation. In two animals, an acrylic well was made around the opening. Electrophysiological recordings were obtained with low-impedance tungsten-in-glass microelectrodes (5 MΩ at 100 Hz), and the neural response was amplified, filtered and monitored through a loudspeaker and an oscilloscope. The electrode was placed perpendicular to the cortical

Table 3
List of abbreviations

Abbreviation	Definition
<i>Cortical areas and regions</i>	
A1	primary auditory area
A2	secondary auditory area
AIP	anterior intraparietal area
IPS	intraparietal sulcus
LIP	lateral intraparietal area
LS	lateral sulcus
M1	primary motor area
MT	middle temporal area
MST	middle superior temporal area
PM	premotor area
PRR	parietal reach region
PV	parietal ventral area
S1	primary somatosensory area
S2	secondary somatosensory area
SMA	supplemental motor area
STS	superior temporal sulcus
V1	primary visual area
V2	secondary visual area
V4	fourth visual area
VIP	ventral intraparietal area
<i>Body parts</i>	
bl	bilateral
d1-d5	digit 1–digit 5
d	dorsal
d d	dorsal digits
d h	dorsal hand
d hl	dorsal hindlimb
dig	digit
el	elbow
fa	forearm
fl	forelimb
ft	foot
glab	glabrous
ha	hand
he	head
hl	hindlimb
l	lateral
m	middle
P1	pad 1
p+d	pads and digits
pr	proximal
r pad	radial pad
sh	shoulder
sn	snout
t pad	thenar pad
u	upper
uvtr	upper ventral trunk
v	ventral
wr	wrist
<i>Tracers and probes</i>	
BDA	biotinylated dextran amine
FB	fast blue
FE	fluoroemerald
FR	fluororuby

surface, and a stepping hydraulic microdrive (Kopf Instruments, Tujunga, CA) was used to lower the electrode in increments of 500 μm into the cortex. The electrode was moved in the x,y -plane in increments of 500 μm with a Kopf micromanipulator. Once the electrode was in place, the body surface was stimulated, and the receptive fields for neurons at that site were drawn on diagrams of the monkey's body. Cutaneous stimulation consisted of light displacements of skin with a fine probe, small puffs of air and light brushing. Light to moderate taps, limb manipulation and pressure were used to

stimulate deep receptors of the muscles, joints and skin. Visual stimulation consisted of full-field flashes of light, bars of light and spots of light moved across the contralateral visual hemifield or flickered within the contralateral visual hemifield. Auditory stimulation consisted of clicks. In all animals, somatosensory, visual and auditory stimulation was used, and the contralateral and ipsilateral body surface, joints and musculature were stimulated. In all animals that received injections of anatomical tracers in areas 3b, 1 or 5, the injection site was electrophysiologically identified prior to perfusion by recording from cortex at and immediately surrounding the center of the injection site.

Selected recording sites in these experiments were marked in one of two ways. First, the recording electrode was dipped in a 7% solution of fast blue and then inserted into the cortex at several sites either on the surface of cortex or into the depths of the IPS (Fig. 7A,B). This method allowed us to readily identify selected electrode penetrations and determine electrode angle for the penetrations into the banks of sulci. Second, we placed electrolytic lesions (10 μA for 10 s) at strategic locations throughout the cortex.

Histology

Upon completion of the electrophysiological mapping session, each animal was transcardially perfused with 0.9% saline, followed by 4% paraformaldehyde in phosphate buffer, and then 4% paraformaldehyde in 10% sucrose phosphate buffer (pH = 7.2–7.4). In one case (case 01-53), 3% paraformaldehyde with 10% sucrose phosphate buffer was used. The brain was removed from the skull, and in six cases, each hemisphere was carefully removed from the underlying thalamus and brainstem. The sulci were gently pried apart, the white matter was undercut, and the cortex was manually flattened and then placed beneath a lightly weighted microscope slide overnight in phosphate buffer with 30% sucrose. The thalamus was placed into phosphate buffer with 30% sucrose overnight. In two cases, whole or half brains were removed and were left intact in phosphate buffer with 30% sucrose overnight prior to sectioning. One additional hemisphere was stored in 10% formalin for 2 months and left intact in phosphate buffer with 30% sucrose overnight prior to sectioning.

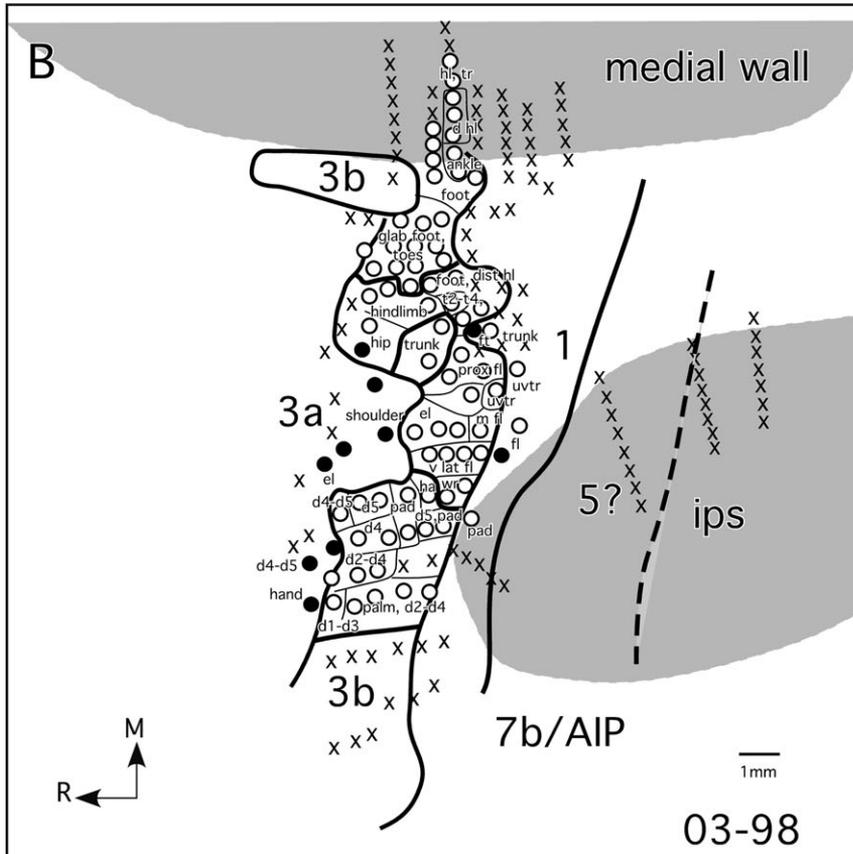
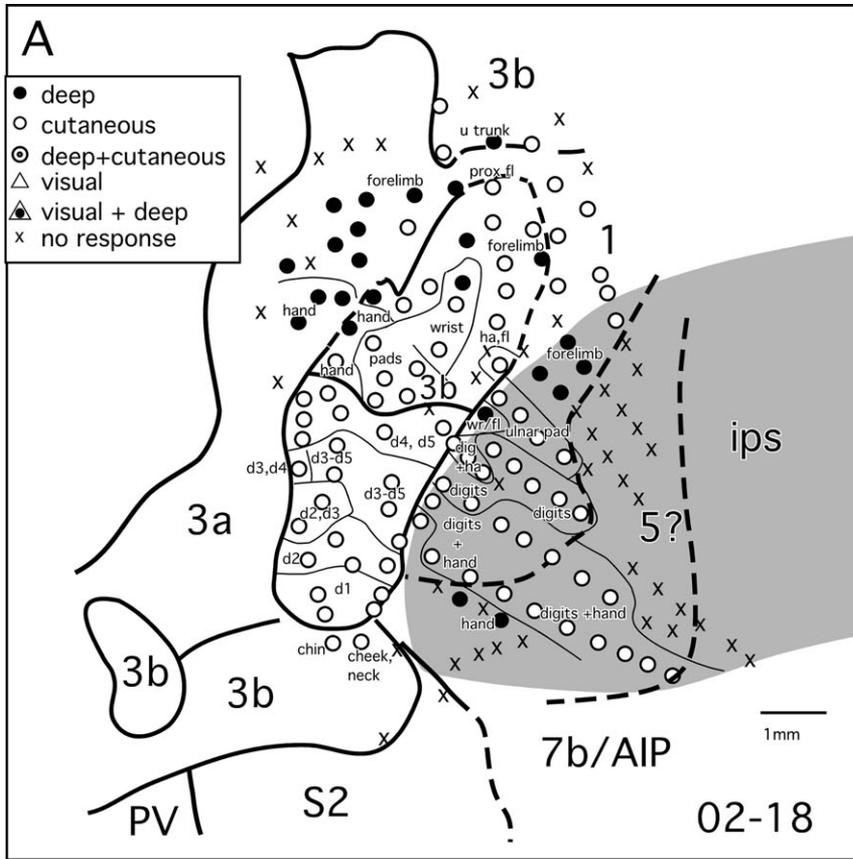
In six cases, the cortical pieces were sectioned tangential to the cortical surface at a thickness of 40 μm for five cases and 30 μm for one case, on a freezing microtome (Table 1). In two cases, the whole brains were sectioned horizontally at a thickness of 60 μm . In one case, one hemisphere was sectioned obliquely at a thickness of 35 μm and stained for myelin. Alternate series of cortical sections were processed for myelin (Gallyas, 1979), mounted for fluorescence microscopy, and/or processed for BDA (Veenman *et al.*, 1992) using standard ABC methods (Vectastain Elite; Vector Laboratories, Burlingame, CA). In the two cases sectioned horizontally, alternate sections were stained for Nissl or myelin.

For cytoarchitectonic comparisons of anterior and posterior parietal cortex in macaque monkeys, we examined four macaque monkey brains that had been used for other experiments. In these monkeys, cortex was sectioned horizontally at 80 μm and alternate sections were stained for Nissl or cytochrome oxidase, or mounted for fluorescent microscopy. Nissl-stained sections were used for comparisons with titi monkeys.

Data Analysis

Data analysis was performed in three separate stages and then all analyzed data were combined into a comprehensive reconstruction. First, the series of sections that were mounted for fluorescent microscopy or processed for BDA were analyzed using an x,y -stage encoding system attached to a computer (Accustage, Inc., Shoreview, MN). For the entire series of sections in each case, labeled cells and injection sites were plotted along with electrode tracks (when visible),

Figure 1. Electrophysiological recording data in areas 3b, 1 and 5?, and neighboring cortex in the flattened left hemisphere of case 02-18 (A) and case 03-98 (B). Neurons in area 3b respond to cutaneous stimulation of the contralateral body, and area 3b is topographically organized with the foot, ankle and trunk represented most medially followed by the representation of the forelimb and hand. The face representation was not well surveyed but is represented far laterally in S1, as has been reported previously for titi monkeys (see Coq *et al.*, 2004). Neurons in area 1, like those in area 3b respond predominantly to cutaneous stimulation of the contralateral body surface, and a rough mediolateral progression could be observed in this field. Most neurons in area 1 were responsive to cutaneous stimulation. All circles, triangles, and crosses denote electrode recording locations. Thick lines represent cortical boundaries determined from myeloarchitectonic analysis, or myeloarchitectonic and electrophysiological analysis combined. Dashed lines indicate cortical boundaries determined from electrophysiological analysis alone. Thin lines mark boundaries between body part representations. Shaded areas mark the IPS and LS. See Table 3 for abbreviations. Medial is up, rostral is to the left.



tissue artifacts, section outlines and fast blue (FB) probes made during the electrophysiological recording stage of these experiments. The resulting series of sections throughout all cortical layers was then combined into a single illustration by aligning injection sites, tissue artifacts and FB probes.

In the second stage of our analysis, electrophysiological maps of the brain were made by analyzing receptive fields and stimulus preference at all sites, and drawing lines which are interpolated between different body part representations. This procedure was more difficult for areas 5 and 3a because receptive fields frequently encompassed multiple body parts. The angle of our electrode penetrations in the rostral and caudal bank of the IPS was determined from sections mounted for fluorescent microscopy and from myelin-stained sections. This was possible because the FB probes and angle of electrode could be readily identified in both series of sections (Fig. 7A,B).

The final stage of our analysis consisted of using a camera lucida to draw architectonic boundaries from the entire series of sections stained for myelin. These sections also included the outline of the section, blood vessels, tissue artifacts, injection sites, FB probes, electrode angles and electrolytic lesions. A single drawing of the cortex was made in a manner similar to that described for analysis of connections. After the three types of data analysis were complete, a comprehensive reconstruction was made by aligning FB probes, lesions, electrode tracks, tissue artifacts and injection sites so that electrophysiological mapping data could be combined with both cortical architecture and patterns of connections. Final drawings and photomicrographs were generated and assembled using Canvas software (ACD Systems, Saanichton, BC) and Adobe Photoshop (Adobe Systems, Inc., San Jose, CA).

Results

Here we describe the electrophysiological recording results in which areas 3b, 1 and cortex caudal to area 1 were mapped in detail, as well as electrophysiological recording results from surrounding regions of cortex which were surveyed less densely. It should be noted that the goal of these experiments was not to determine the neural response properties of neurons. Response properties of neurons in posterior parietal cortex (caudal to area 1) are undoubtedly affected by anesthesia. Our goals for these electrophysiological recording experiments were to determine if titi monkeys have areas 1 and 2, using methods similar to those used to identify these anterior parietal fields in macaque monkeys, and to determine the receptive fields for neurons at our injection sites, and to determine the location of our injection sites relative to cortical field boundaries. We combine these results with an analysis of cortical myelo- and cytoarchitecture. Finally we describe the ipsilateral and contralateral connections of areas 3b, 1 and cortex caudal to area 1.

The Organization of Anterior Parietal Areas 3b, 1 and 3a

Area 3b

Electrophysiological recordings in area 3b (Figs 1A,B, 2A; 01-79 and 02-12 not shown) demonstrate that neurons respond to cutaneous stimulation of the contralateral body and that the receptive field size for neurons was small (Figs 3-5), like that described for receptive fields of neurons in area 3b of other primates as well as other mammals (reviewed by Merzenich

et al., 1978; Nelson *et al.*, 1980; Sur *et al.*, 1982; Krubitzer, 1995). In terms of topographic organization, a progression of receptive fields from tail, foot, hindlimb, trunk, forelimb, digits and face was observed as recording sites progressed from medial to lateral in the cortex (Fig. 4). Although we only encountered neurons at one recording site with receptive fields on the tail and could not identify a complete tail representation electrophysiologically, a myeloarchitectonic region that was contiguous to the representation of area 3b on the dorsal surface was located on the crown of cortex that forms the medial wall. It is likely that the tail representation resides here, but is difficult to access with our recording electrode. In the three cases in which electrophysiological recordings were made in the medial portion of area 3b on the dorsal surface just lateral to the medial wall, the foot and toes were represented (e.g. Fig. 1B, 01-79 and 02-12 not shown). Lateral to the representation of the foot and toes was the representation of the hindlimb and trunk followed by the representation of the forelimb. The hairy hindlimb, trunk representations and forelimb representations occupied a relatively large portion of the entire field — about the same amount as that occupied by the representation of the hand. Lateral to the representation of the forelimb was the representation of the hand. Within the hand representation, receptive fields for neurons moved from D5 to D1 in a mediolateral progression of recording sites (e.g. Figs 1A,B, 5D,F).

Area 1

Electrophysiological recordings were made just caudal to area 3b in all cases. In four cases, neurons in this region responded predominantly to cutaneous stimulation of the contralateral body surface (Figs 1A, 2A,B), and in three cases, neurons responded to more vigorous stimulation of the contralateral body, or were unresponsive to any type of sensory stimulation under our recording conditions (e.g. Fig. 1B). When the overall topography of this region is examined and considered with respect to cortical cyto- and myeloarchitecture and connectivity, we believe this field is homologous to area 1 described in other New World monkeys and macaque monkeys (see Discussion).

The mediolateral organization of area 1 was much like that of area 3b in that the face, lips and chin were represented most laterally in the field, followed by the representation of the digits, hand, forelimb and trunk in a lateromedial progression (Fig. 5A,C). However, only in one case was the face representation explored (Fig. 2A). In the other cases, cortex lateral to the hand representation, in the expected location of the face representation, contained neurons that were unresponsive to any type of sensory stimulation under our recording conditions. In all cases, the representation of the digits in area 1 was identified. The digits were not represented individually, but rather several digits were represented together, or with the entire hand (Fig. 3B), unlike area 3b or area 1 in some other New World monkeys and macaque monkeys. Medial to the representation of the digits was the representation of the forelimb, and then the representation of the trunk.

Figure 2. Electrophysiological recordings in areas 3a, 3b, 1 and 5?, and neighboring cortex in the flattened left hemisphere of cases 01-53 (A) and 02-52 (B). In these cases, cortex caudal to area 1 was mapped in more detail than the cases in Figure 1. Area 5? was dominated by representations of the digits, hand and forelimb. A loose topography was observed mediolaterally within area 5?, with the trunk represented medially, followed by proximal forelimb. More laterally, distal forelimb, hand and digits were represented. In both cases, sites were observed in which groups of neurons responded to stimulation of deep receptors and visual stimulation. Note that the organization of area 3b is topographically precise while that of areas 1 and 5? are less precise and dominated by the representations of the hand and forelimb. All conventions are as in Figure 1.

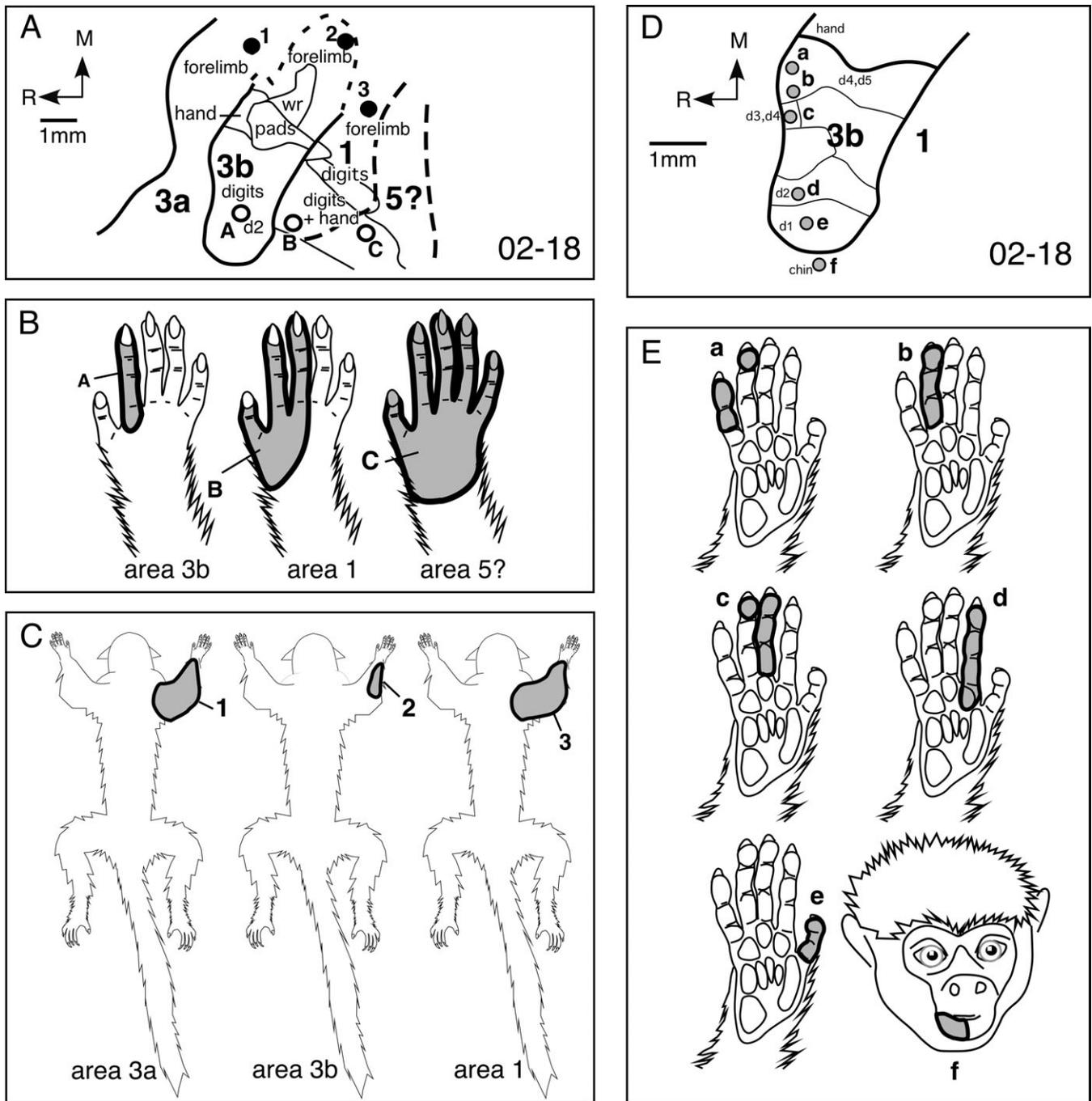
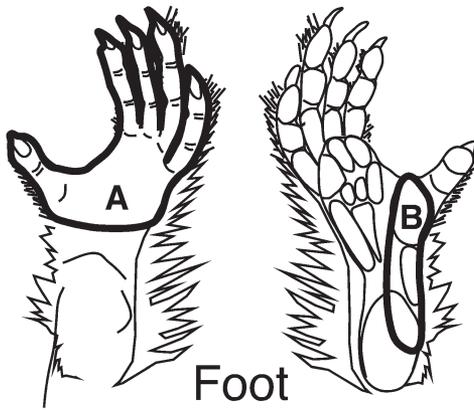
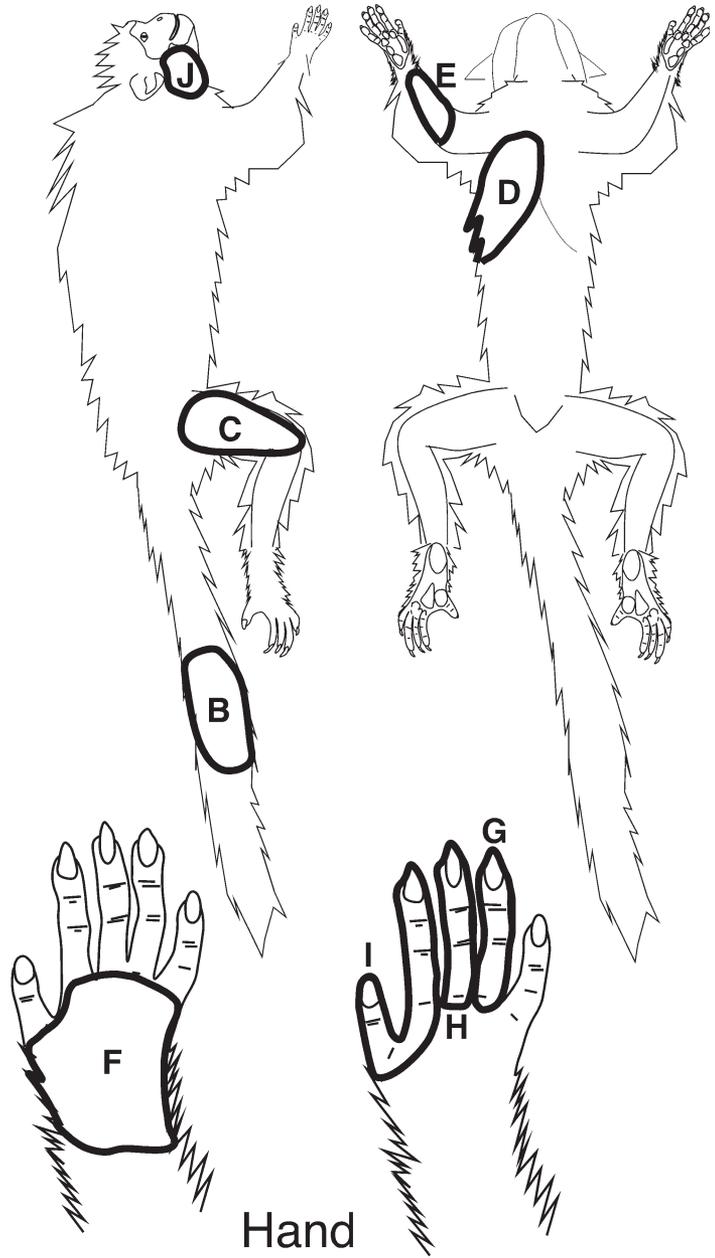
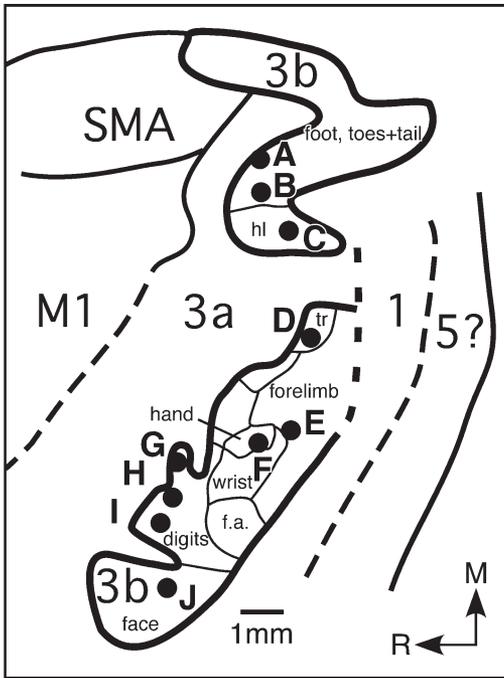


Figure 3. Electrophysiological recordings in areas 3a, 3b, 1 and 5? (A, D), and corresponding receptive fields for neurons at those sites in areas 3b, 1 and 5? (B), areas 3a, 3b and 1 (C), and area 3b (E). This figure illustrates that receptive fields for neurons in area 3b are relatively small, and often limited to a single digit (panel B, receptive field A; and panel E). Receptive fields in areas 1 and 5? for the same portion of the hand are much larger and incorporate several digits or all digits. Conventions as in previous figures.

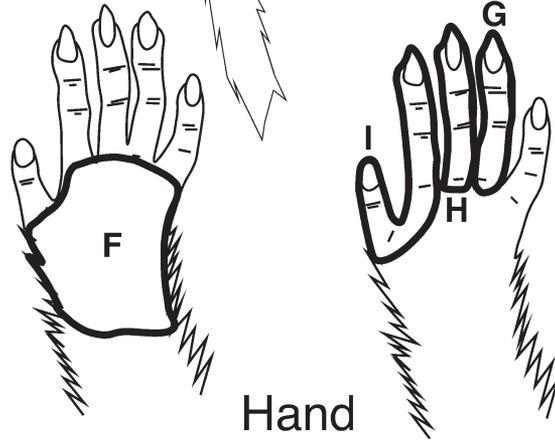
In three cases, some neurons in the forelimb (Fig. 2) and digit representations (01-79 not shown) also responded to visual stimulation. In one case (Fig. 2B), neurons at three recording sites had bilateral receptive fields on the trunk (Fig. 5C). Cortex medial to the representation of the forelimb was in most cases unresponsive to any type of stimulation under our recording conditions. Immediately caudal to area 1, neurons responded to stimulation of deep receptors of the forelimb and hand, and in some instances to visual stimulation. We term this field the presumptive area 5 for several reasons discussed below.

Area 3a

In all cases, recording sites were made just rostral to area 3b, in area 3a. Although in most cases the number of recording sites was limited, there were several consistent observations. First, when all cases are considered together, the general topographic organization of area 3a mirrored that of area 3b in that the toes, foot and hindlimb were represented medially in the field, while the shoulder, forelimb, hand and digits were represented more laterally in the field (e.g. Figs 1A,B, 2A). The second observation was that most neurons in area 3a responded to stimulation of



01-79



Hand

Figure 4. Electrophysiological recordings (inset) and corresponding receptive field progressions in area 3b for case 01-79. A progression of recording sites (top left) from medial to lateral in 3b corresponds to a receptive field progression from foot/tail medially (A, B) to the leg, trunk, forelimb, hand and chin laterally (C–J). Note that topography in 3b is precise. Conventions as in previous figures.

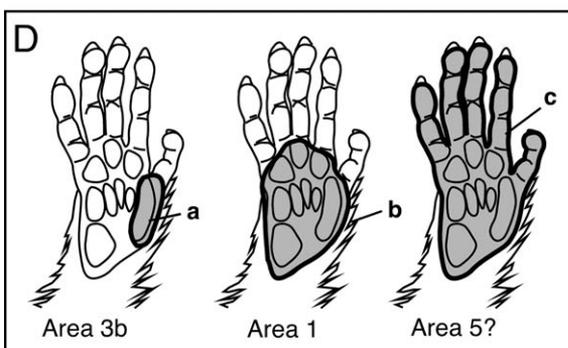
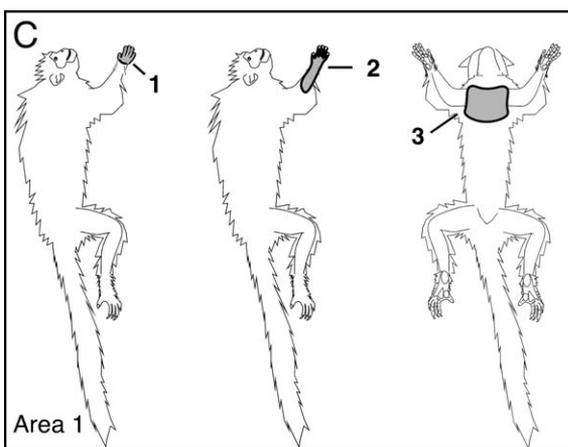
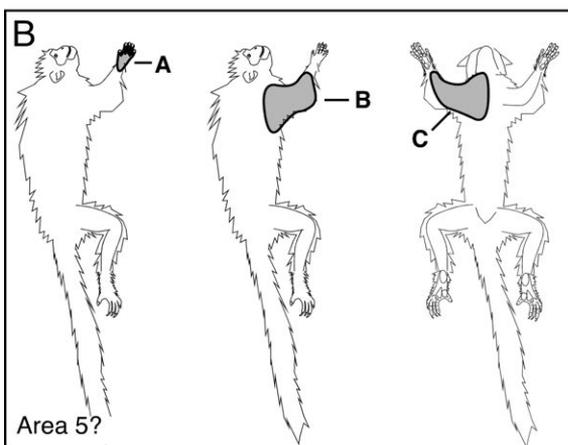
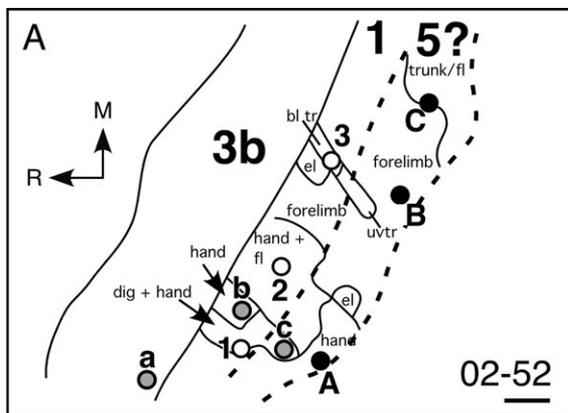
deep receptors of the contralateral body. Finally, neurons in area 3a had relatively large receptive fields compared to neurons in area 3b (Fig. 3C).

The Organization of Cortex Caudal and Caudolateral to Area 1

In all cases, cortex immediately caudal to area 1 was located on the rostromedial bank of the IPS and was adjacent to the caudal border of the digit and hand representation in area 1, as defined electrophysiologically and architectonically. Neurons in cortex caudal to area 1 were often difficult to drive under our recording conditions and stimulation methods. However, in most cases neurons in this region were responsive to high-threshold somatic stimulation, which could be due to stimula-

tion of deep or cutaneous receptors. Further, a number of recording sites contained neurons that were unresponsive to any type of stimulation. This finding is in contrast to anterior parietal areas 3a, 3b and 1 in titi and other New World monkeys examined, and to area 2 in macaque monkeys (Merzenich *et al.*, 1978; Nelson *et al.*, 1980; Sur *et al.*, 1982; Felleman *et al.*, 1983; Coq *et al.*, 2004). In particular, neurons in area 2 in macaque monkeys respond well under similar recording conditions (see Pons *et al.*, 1985; Disbrow *et al.*, 2000).

Partial or nearly complete maps of the region caudal to area 1 were obtained in four cases. In two cases all neurons were driven by taps to the body and joint manipulation (Fig. 2A, case 01-79 not shown), in one case about two-thirds of the neurons were driven by taps to the body and joint manipulation and the



remaining neurons were driven by stimulation of cutaneous receptors (Fig. 2B), and in one case neurons which were responsive to somatic stimulation were predominantly driven by cutaneous stimulation (Fig. 1A). In the latter cases, the representation of cutaneous receptors formed a peninsula adjacent to the caudal border of area 1 (Fig. 2B), and receptive fields for neurons at these sites were on the hand. In three cases (Fig. 2A,B; 01-79 not shown), neurons were driven by visual stimulation, although no systematic mapping of receptive fields was attempted (see Materials and Methods). In one case, all recording sites in which neurons responded to visual stimulation were bimodal in that they also responded to somatic stimulation (Fig. 2B). In this case, all of these recording sites had receptive fields on portions of the forelimb or trunk. In the two other cases bimodal visual/somatic recording sites were observed as well as recording sites in which neurons responded to visual stimulation alone (Fig. 2A; 01-79 not shown). In these two cases, receptive fields for neurons at these bimodal sites were on the digits, hand and/or forelimb. We believe the variability in stimulus preference and responsiveness was largely an anesthetic effect, which is often the case with higher-order cortical areas.

Receptive fields for neurons in cortex caudal to area 1 were generally larger than those in areas 3b and 1 (Figs 3 and 5) and encompassed several digits, the entire hand, the entire forelimb, or the entire forelimb plus the hand (Fig. 5). In all cases, we systematically stimulated the contralateral and ipsilateral body during our recordings. Bilateral receptive fields were identified in two cases. In one case, bilateral receptive fields were found on the forelimb and hand (01-79 not shown), and in one case bilateral receptive fields were on the trunk (Fig. 2B).

When all cases are considered, a mediolateral progression of receptive fields demonstrated a loose topographic organization for this area of cortex with the trunk and proximal forelimb represented medially in the field followed by the distal forelimb and elbow (Figs 1-3 and 5). Lateral to these representations was the representation of the hand, wrist and digits, with the representation of the chin and lips in the most lateral portion of the field. The most common feature of this area in all cases was the cortical magnification of the digits, hand and forelimb representations. In two cases (Fig. 2), the representation of the digits/hand/forelimb occupied over one-half of the entire mapped area. The hand and forelimb representation was identified in two of the other cases, but the mapping density was lower (01-79, 02-12, not shown) and neurons in these cases in medial portions of this area were unresponsive to any type of stimulation under our recording conditions. Within the representation of the hand, multiple digits were represented together (Fig. 3B), so that topography could not be discerned. In three cases, a forelimb and/or shoulder representation was observed, and was located medial to the representation of the

Figure 5. Electrophysiological recordings in areas 5? and 1 (A), and corresponding receptive field progressions for neurons in area 5? (B), area 1 (C), and across areas 3b, 1 and 5? (D). As recording sites move from lateral to medial in both areas 1 and 5?, receptive fields for neurons at those sites move from the hand to the proximal forelimb. In area 5?, many neurons respond to stimulation of deep receptors. In area 1, most neurons respond to cutaneous stimulation (open circles) and in some instances, neurons have bilateral receptive fields (receptive field C3). As recording sites in glabrous representations move caudally from area 3b, to area 1, to area 5?, the receptive fields for neurons at those sites increase in size (D). Conventions as in previous figures.

digits and palm (Fig. 5A,B). In three cases, several separate forelimb representations were observed (e.g. Fig. 2A).

In most of our maps of this caudal area we did not observe body part representations other than the hand and forelimb. Although much of cortex on the rostral bank was explored in these cases, there was no response in neurons medial to these representations (e.g. Fig. 2A,B). In one case in which neural responses could be elicited medial to the forelimb representation, the representations of the shoulder and upper trunk were observed (Fig. 2B). In one case, we were able to elicit responses from neurons in this area by stimulating the chin, lips and snout, each of which were represented separately within the field (Fig. 2A). Taken together, we believe the electrophysiological recording data indicates that this field is like area 5 described in macaque monkeys, rather than like area 2 (see Discussion). Therefore we term this area the presumptive area 5, or area 5?

Electrophysiological recordings were also made just caudal and/or caudolateral to the presumptive area 5 in five cases, on the lower or caudal bank of the IPS and on the inferior parietal lobule. Most neurons in these regions of cortex were unresponsive to any type of stimulation under our recording conditions. The cortex immediately caudal to the presumptive area 5 is in the location of LIP and VIP of macaque monkeys, while cortex located more laterally is in the location of area 7b and AIP. In two of the three cases neurons in area 7b/AIP that did respond to stimulation under our recording conditions responded to visual stimulation (Fig. 2A; 01-79 not shown). In these cases, there was no attempt to determine visual receptive fields for neurons at these sites. Likewise in the three cases in which neurons in the LIP/VIP region did respond to stimulation, they responded predominantly to visual stimulation. We term the field caudolateral to area 5? area 7b/AIP and the area of cortex caudal to area 5? LIP/VIP, based on location, limited electrophysiological recordings and some aspects of connectivity; however, the status of homology of these field with fields in the macaque monkey is uncertain.

Cortical Myeloarchitecture

In all cases, electrophysiological recordings were related to myeloarchitectonic distinctions by matching lesions and probes placed during electrophysiological recording sessions to the entire series of sections that were stained for myelin. There were a number of boundaries that could be reliably identified architectonically and related to functional boundaries determined from electrophysiological recording experiments. The most consistently identified fields were areas 3b, 3a and 1. The myeloarchitecture of area 3b in the titi monkey is similar to that described for a number of primates and non-primate mammals (e.g. Krubitzer and Kaas, 1990a; Disbrow *et al.*, 2003; see Krubitzer, 1995). Area 3b stains darkly for myelin, particularly in the middle cortical layers (Fig. 6A). Also, like other mammals, the myeloarchitecture of area 3b is not homogeneous, but rather is composed of a number of myelin light and dark regions, similar to those described for marmosets (Krubitzer and Kaas, 1990b), flying foxes (Krubitzer *et al.*, 1998) and owl monkeys (Jain *et al.*, 2001). The myelin dark regions of area 3b are related to islands of neurons which respond to cutaneous stimulation of the contralateral body, while the myelin light regions appear to separate major body part representations, such as the hand and the face (e.g. Fig. 6A; see also Fig. 1A,B). In flying foxes, we

argued that these myelin light, invaginated regions were portions of adjacent fields (Krubitzer and Calford, 1992), including area 3a, and this appears to be the case for the titi monkey as well.

Area 3a, which borders area 3b rostrally, was moderately myelinated and coextensive with neurons that responded to stimulation of deep receptors of the contralateral body. Area 3a was bounded rostrally by a darkly myelinated area 4 or M1. Immediately caudal to area 3b was a moderately myelinated field that was coextensive with neurons that responded to somatic stimulation. We termed this field area 1 because of similarities with area 1 in some other New World monkeys and macaque monkeys (see Discussion). The medial and lateral boundaries of this field were often difficult to distinguish architectonically, and in most cases were not designated, or were designated with a dashed line that was determined using electrophysiological responses. The presumptive area 5 was located in the upper bank of the IPS directly caudal to area 1, and was densely myelinated in the middle cortical layers. In the section shown (Fig. 6A) the light staining in area 5? is due to curvature of the tissue into the IPS, such that only more superficial layers are visible. The caudal border of area 5? was difficult to determine architectonically, and is designated with a dashed line. A moderately myelinated field, which we have termed area 7b/AIP (see Discussion), was located lateral to the lower bank of the IPS, and was coextensive in two cases with neurons that responded to visual stimulation.

In order to establish which cortical fields were interconnected with those injected, it was necessary to identify the boundaries of cortical fields other than those mapped using myeloarchitectonic criteria. While not much is known about the organization and architecture of titi monkey neocortex, a number of studies in other New World monkeys have related electrophysiologically defined cortical fields to cortical myeloarchitecture in visual (e.g. Krubitzer and Kaas, 1990a), auditory (Luethke *et al.*, 1989), somatosensory (Krubitzer and Kaas, 1990b; Huffman and Krubitzer, 2001) and motor (Stepniewska *et al.*, 1993; Huffman and Krubitzer, 2001) cortex. We use the descriptions of many of these boundaries identified previously to help us subdivide the neocortex of the titi monkey using myeloarchitecture.

Cortical Cytoarchitecture

Cytoarchitectural boundaries of anterior and posterior parietal cortex were identified using standard Nissl staining in horizontal sectioned tissue in two cases. Area 3b had a very dense staining pattern in cortical layers II–IV, with a prominent layer IV (Fig. 6B). Area 1 was directly caudal to area 3b, near the lip of the upper bank of the IPS, and had a less prominent layer IV, and generally had a more diffuse staining pattern within layers II and III than area 3b (Fig. 6B,E). The boundary between areas 3b and 3a was marked by a very thin, reduced layer IV in area 3a, and a pronounced layer V in area 3a (Fig. 6B,D). To facilitate comparisons of cytoarchitectonic borders of anterior and posterior parietal cortical areas, we examined macaque monkey cortex that was sectioned in a similar plane and stained for Nissl (Fig. 6C). We observed that areas 3a, 3b and 1 could be easily identified in both species, and that the features described above for these areas in titi monkeys were remarkably similar in macaque monkeys.

Comparisons became less secure once cortex caudal to area 1 was compared in both species. In titi monkeys, the boundary of

the presumptive area 5 with area 1 was observed within the upper bank of the IPS as a decreased intensity of staining within layer IV and a thickening of layers II–III (Fig. 6B,F). The caudal boundary of area 5? (deep in the sulcus) was less clearly demarcated, but was noted as a decrease of staining intensity in layer IV. Caudal to area 1 in macaques, layers IV and VI in area 2 were observed to be thicker as compared to area 1, and darkly staining (Fig. 6C). Such a field is not observed in titi monkeys. Immediately caudal to area 2, area 5 was observed to have thinner and less intensely stained layers IV and VI, and like titi monkeys, a thicker layer II and III. The caudal boundary of area 5 in macaques, like titi monkeys, was more difficult to determine. However, we did note a decrease in the staining intensity of layers IV and VI.

Cortical Connections

In four animals, two injections were made in area 3b, three injections in area 1, three injections in presumptive area 5 and two injections in area 7b/AIP (Table 2; Fig. 7C–H). In most of these cases, extensive electrophysiological recordings around the injection sites allowed us to define the receptive field for neurons at the injection site, as well as to appreciate the details of how different body part representations were interconnected. In the following section, we first describe the ipsilateral connections of areas 3b, 1, and presumptive areas 5 and 7b/AIP with electrophysiologically defined fields surrounding the injection site, and the overall patterns of ipsilateral connections of these fields. We then describe the callosal connections of these fields.

Ipsilateral Connections of Areas 3b and 1

Small injections of neuroanatomical tracers were made in area 3b in 2 cases (Fig. 8A,8B). In one case, FE was injected in the P1 representation of area 3b (Fig. 8A), and in the other case BDA was injected in the d2 nail bed representation (Fig. 8B). The patterns of retrogradely transported tracer were similar for both cases. Intrinsic connections immediately around the injection site in P1 in case 02-12 were observed in the electrophysiologically identified representation of the dorsal hand and the forelimb representations of area 3b (Fig. 8A). Labeled cells were also observed in the expected location of the face representation in 3b. In area 3a, labeled cells were observed in the representations of the digits, hand, shoulder, forelimb, neck and the expected location of the face representation. Retrogradely labeled cells in area 5? were found in the expected location of the hand and digit representations, and labeled cells in area 1 were observed in the representations of the digits, hand and forelimb. For the injection in the d2 nail bed representation (Fig. 8B), labeled cells were observed around the injection site in the representations of the pads, the dorsal digits and the glabrous digits. Although area 3a was not mapped in this case, dense label was observed in the same mediolateral location as that in 3b, in the expected location of the hand and forelimb in area 3a. Label in area 1 was sparse and in a similar mediolateral location as that in area 3b, in the representation of the digits. Labeled cells in area 5? were in the electrophysiologically identified portion of the forelimb and upper trunk representations. Labeled cells were consistently observed in other cortical areas, including S2, PV and M1. In one case, labeled cells were also observed in cingulate cortex.

The three cases in which the injection sites were placed in the electrophysiologically defined hand representation of area 1

had remarkably similar patterns of local connections (Fig. 9; 02-12 FR not shown). Surprisingly, only a few cells were observed in areas 3b and 3a. Labeled cells in area 3b were observed in the representation of D1, and the expected location of the face and trunk representation. Labeled cells in area 3a were found at the same mediolateral level as those in area 3b. For all cases, labeled cells in portions of area 5? were sparse, and scattered throughout the field. Labeled cells from the injection centered in the hand and forelimb representation (Fig. 9A) were observed in the representation of the hand, digits, upper ventral trunk, forelimb and trunk representations in area 5?. The injection into the cutaneous representation of the digit and hand in area 1 in case 02-18 spread into area 5? (Fig. 9C). Despite the spread into area 5?, the pattern of connections was similar to the other two injections in area 1 that were restricted (rather than similar to area 5? connections), suggesting that the effective uptake zone was in area 1.

The overall pattern of connections for area 1 was similar across cases, and dramatically different from the connections of areas 3b, 5? and 7b/AIP (compare Figs 8–11). In addition to the connections described above, in all three cases labeled cell bodies were also observed in 7b/AIP, LIP/VIP, S2, M1, PM and frontal cortex. In all cases, a few labeled cells were also observed in the superior temporal sulcus (not shown), and in two cases in cingulate cortex (e.g. Fig 9B).

Ipsilateral Connections of Cortex Caudal and Caudolateral to Area 1

Presumptive area 5. Three injections were made in area 5?. Two injections were completely restricted to area 5? (Figs 10D,E, 11A,C); one injection spread slightly into the digit and hand representation of area 1 (Fig. 10A). In case 02-18, an injection of FE was centered in the representation of the hand in area 5? (Fig. 10A), and in case 01-79, the injection site of FE was not completely mapped, but nearby recording sites contained neurons with receptive fields on all digit tips (Fig. 11A–C). In these cases, electrophysiological recordings were made throughout area 5? and adjacent fields 3b, 1 and 3a. Labeled cell bodies were related to electrophysiological and/or architectonically defined cortical fields.

For these cases, labeled cell bodies were observed throughout area 5? in the representations of the digits, hand and forelimb, and medially in cortex in which neurons were unresponsive to any type of stimulation under our recording conditions. Labeled cell bodies were observed in area 3b in all cases in the representations of the digits, other portions of the hand and forelimb. For all cases, label was also observed in the representations of the trunk, foot and toes, but the density of label in these representations in area 3b varied. Labeled cell bodies were identified in area 1 in all cases. Like 3b, label in area 1 was observed throughout portions of the hand and forelimb representation. Retrogradely labeled cell bodies were also observed medially in area 1, in the expected location of the trunk and hindlimb representations. Finally, in all cases, label was observed throughout the mediolateral extent of area 3a, but in two cases it was most dense in the representation of the hand and forelimb (Figs 10F and 11A).

The overall pattern of connections of the presumptive area 5 was also determined (Figs 10 and 11). Dense connections were observed with cortex immediately adjacent to the injection site, with S2, PV, M1, PM, 7b/AIP and LIP/VIP. Finally, in all cases

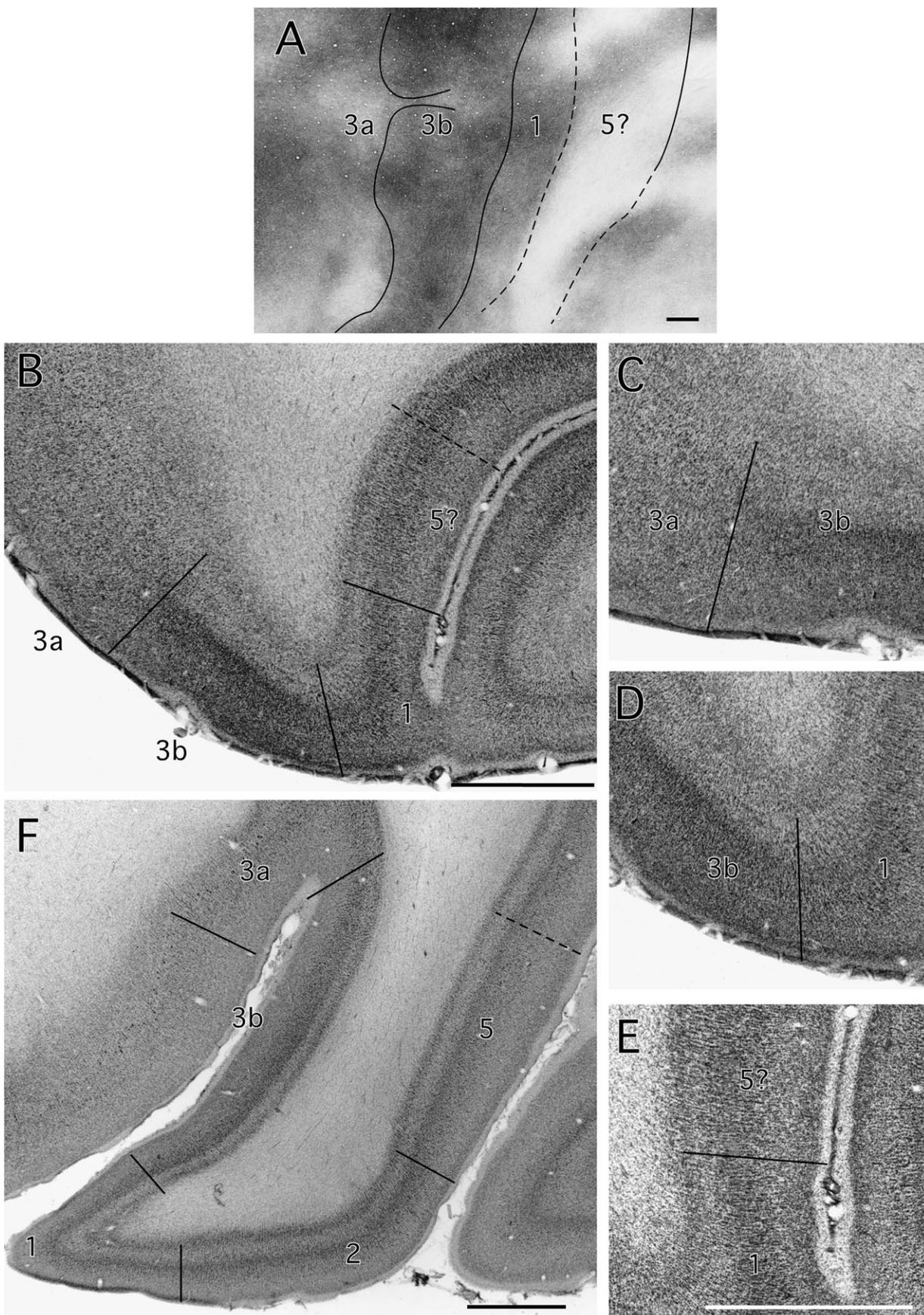


Figure 6. Myeloarchitecture and cytoarchitecture of areas 3b, 1, and 5?. (A) Light-field photomicrograph of cortex that has been flattened, cut parallel to the cortical surface, and stained for myelin (A: case 03-98). The myeloarchitecture of area 3b is not homogeneous, but rather is composed of a number of myelin light and dark regions. The myelin dark

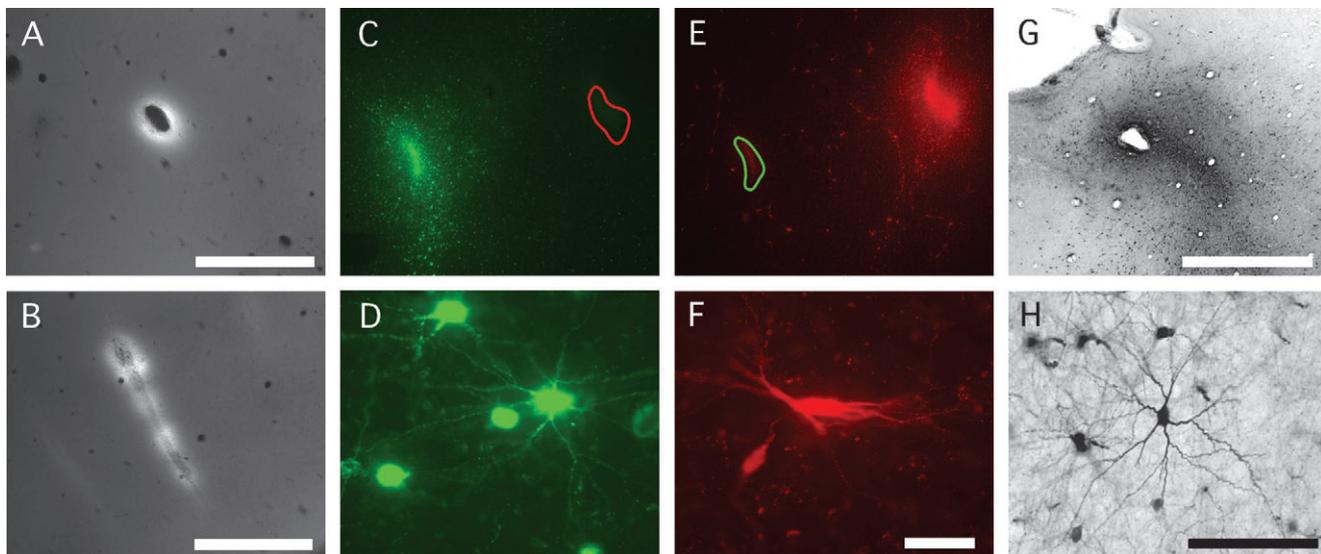


Figure 7. Fluorescent probes, tracer injections and resultant label in cortex that has been flattened and sectioned tangentially. (A) Electrode penetration on the cortical surface, marked with Fast Blue and visualized under fluorescent illumination. (B) Electrode penetration along the upper bank of the IPS, marked with Fast Blue and visualized under fluorescent illumination. Note that angle of electrode is easily discernible with this technique. (C, D) Injection site of FluoroEmerald in case 01-79, and representative labeled cells from the same case. Red outline in panel C indicates injection of FluoroRuby that is shown in E. (E, F) Injection site of FluoroRuby in case 01-79, and representative labeled cells from the same case. Green outline in panel E indicates injection of FluoroEmerald that is shown in panel C. (G, H) Injection site of BDA in case 02-18, and representative labeled cells from the same case. Scale in A–C, E and G is 500 μ m. Scale in D and F is 50 μ m. Scale in H is 100 μ m.

scattered labeled cells were observed in the superior temporal sulcus as well as on the gyrus caudal to STS.

Area 7b/AIP. Injections of BDA were made in area 7b/AIP in two cases (Fig. 12A,B). These injections were made relative to sulcal patterns and the injection sites were not mapped, although in one case, nearby cortical fields such as areas 5?, 3b, 1 and 3a were explored electrophysiologically. In this case (Figs 1A and 12A), an injection in area 7b/AIP resulted in label in the hand, digits and forelimb representation of area 5?. A few cells were in the digit representation of 3b, in the upper trunk representation of area 3b, and in the hand and forelimb representation of area 3a. The overall pattern of label was similar in the other case in which BDA was injected into area 7b/AIP. Only a few scattered cells were observed in areas 3b, 3a and 1. Label in area 5? was moderately dense. Very dense label was observed surrounding the injection site, in other portions of area 7b/AIP, and in areas S2, cortex lateral to S2 and PV, and auditory cortex. Labeled cells were also observed in LIP/VIP, cingulate cortex and in the STS. Label in M1 was very sparse in

each case, however, in both cases label in PM was moderate to dense (Fig. 12A,B).

Callosal connections. Connections with the opposite hemisphere were observed for one of the injections in 3b (Fig. 13A), one of the injections in area 1 (Fig. 13B), for all of the injections in area 5? (Fig. 13C) and for one of the injections in area 7b/AIP (Fig. 13D). All injections in areas 3b, 1 and 5 in the ipsilateral hemisphere were made into portions of the hand representation. The FE injection into the caudolateral portion of 3b, in the representation of P1 (Fig. 8A), resulted in sparse label medially in 3b, in the expected location of the forelimb in the opposite hemisphere (Fig. 13A). Sparse label was also observed in the lateral portion of area 1 and S2 of the opposite hemisphere. Finally, a few cells were observed in area 5? and LIP/VIP in the opposite hemisphere. The injection of BDA into the nail bed representation of 3b (Fig. 8B) did not produce any label in the contralateral hemisphere.

The injection into the hand + forelimb representation in area 1 (Fig. 9A) resulted in sparse label in the contralateral hemisphere

regions of area 3b are related to islands of neurons which respond to cutaneous stimulation of the contralateral body, while the myelin light regions appear to separate major body part representations, such as the hand and the face, and correspond to regions in which neurons respond to stimulation of deep receptors of the contralateral body (e.g. Fig. 1A,B). Further, these myelin light region are reciprocally interconnected with the opposite hemisphere. Area 3a, which borders area 3b rostrally, was moderately myelinated and coextensive with neurons that responded to stimulation of deep receptors of the contralateral body. Area 3a was bounded rostrally by a darkly myelinated area 4 or M1. Immediately caudal to area 3b was a moderately myelinated field that we termed area 1. Area 5? was located directly caudal to area 1 and was densely myelinated in the middle cortical layers, although this is less evident in the section shown due to curvature of the tissue into the IPS. (B) Light-field photomicrograph of cortex that has been sectioned horizontally and stained for Nissl substance in a macaque. Area 3b was observed to have a dense staining pattern in cortical layer IV. Directly caudal to area 3b, area 1 was observed to have a less prominent layer IV. The boundary of area 5? with area 1 was observed within the IPS as a decreased intensity of staining within layer IV, and a thickening of layers II–III. The caudal boundary of area 5? was less clearly demarcated. (C–E) High power photomicrographs of section shown in panel B indicating the border between area 3a and 3b (C), between area 3b and 1 (D), and between area 1 and area 5? (E). F. Light-field photomicrograph of cortex that has been sectioned horizontally and stained for Nissl substance in a macaque. Area 3b was observed to have a dense staining pattern in cortical layers II–IV, as in titi monkeys. Directly caudal to area 3b, area 1 was observed to have a less prominent layer IV. Caudal to area 1, area 2 was observed to have thicker and more densely stained layers IV and VI. This cytoarchitectonic distinction is not observed in titi monkeys. The boundary of area 5 with area 2 was observed as a decreased thickness and intensity of staining within layer IV and VI, and a thickening of layers II–III, as in titi monkeys. The caudal boundary of area 5 was less clearly demarcated, but was noted as a decrease of staining intensity in layer IV. In all panels, rostral is to the left, and black lines mark architectonic boundaries. Scale bar in panel A is 1 mm. Scale bar is 2 mm in panels B–F (scale in panel E applies to C–E).

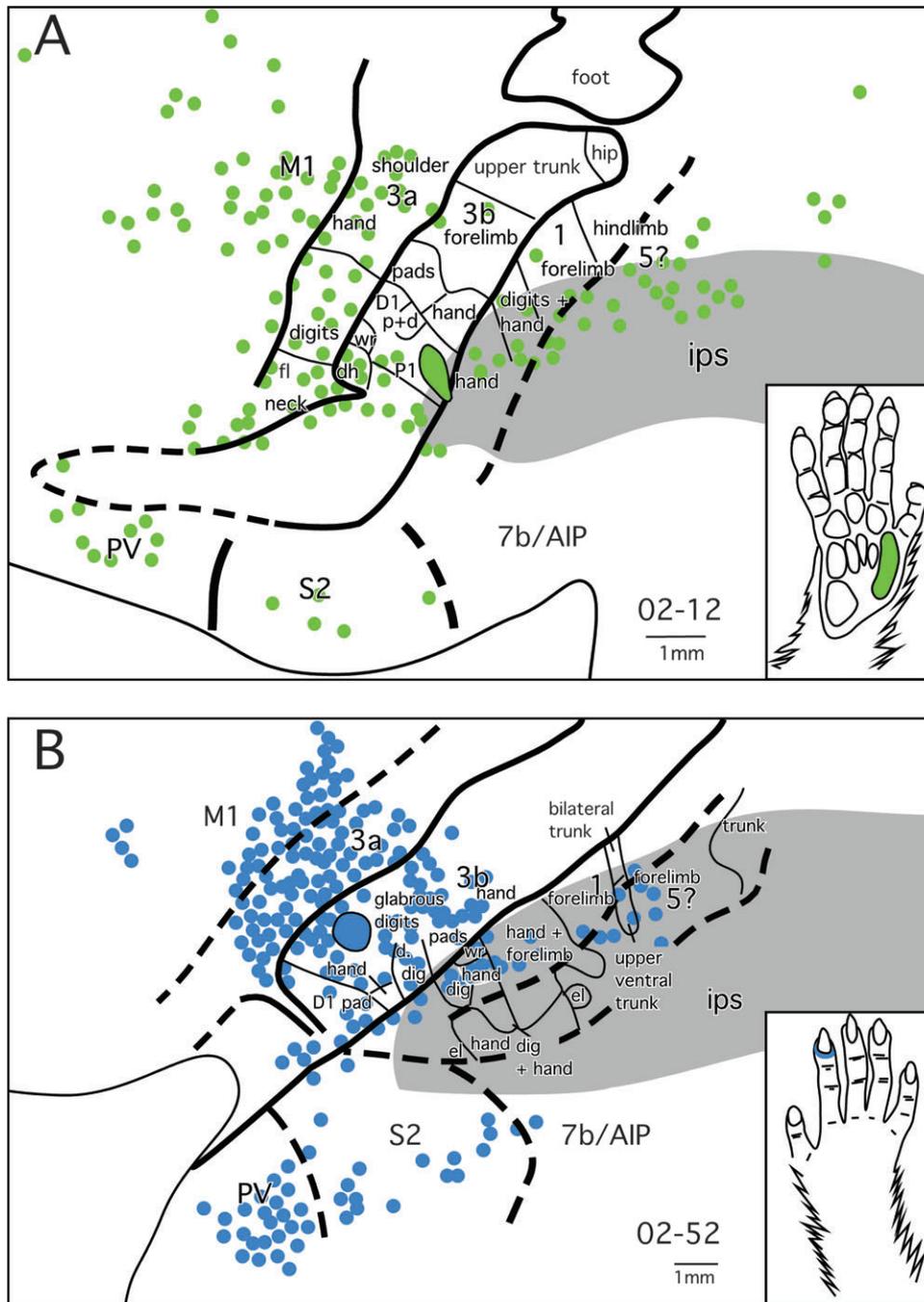


Figure 8. Ipsilateral connections of area 3b. (A) Tangential reconstructions of label observed following injection of FE at the representation of P1 in case 02-12. Intrinsic connections surrounding the injection site in P1 were observed with representations of the dorsal hand, forelimb and face in area 3b. Connections were also observed in the digits, hand and forelimb representations in areas 1 and 5?. The ipsilateral connections of area 3b were much more restricted than those of area 5? or 7b/AIP (see Figs 10–12), and the label was observed to be most dense in areas 3a and M1. Injection of FE near the representation of the glabrous D1 tip representation in case 02-52 (B). Conventions as in previous figures.

in the lateral portion of area 1, in S2, PV, area 5?, 7b/AIP, and premotor cortex of the opposite hemisphere (Fig. 13B). Of note is that in the two cases with the injection into the hand and digit representation in area 1 that did not include portions of the forelimb, there was no label in the contralateral hemisphere.

All three injections into the hand/digit representation in area 5? (Figs 10A,D and 11B) produced dense label in the opposite hemisphere. In these three cases, labeled cells were most dense in areas 5?, 7b/AIP, S2 and PV, and conspicuously absent in the expected location of the hand representation of areas 3b and 1

(Fig. 13C; 02-52 and 02-18 not shown). Thus, sensory inputs from both hands converge in area 5?. Less dense connections were observed in cortex just caudal to area 5?, in premotor cortex and in cingulate cortex. Finally, one of the injections in 7b/AIP resulted in dense label in 7b/AIP in the opposite hemisphere, in caudal portions of the IPS, and a few scattered cells in PM and cingulate cortex (Fig. 13D).

The presence of contralateral label in some cases but not others could be attributed to several factors. The first is a lack of transport of a particular tracer. We do not believe this to be the

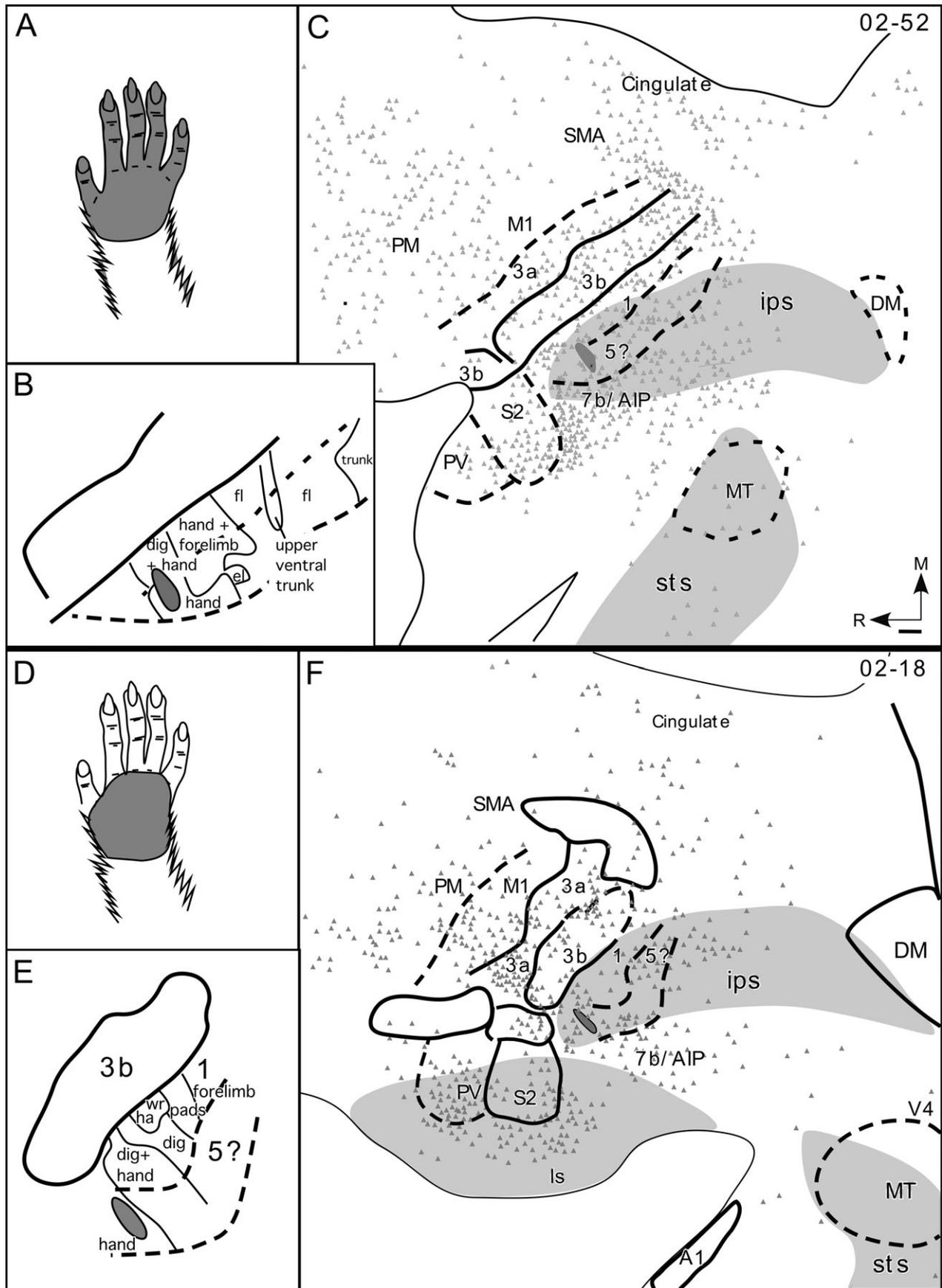


Figure 10. Tangential reconstructions of injections of FE in area 5? (C, F) at the representation of the hand in cases 02-52 (A) and 02-18 (i). Extensive connections were observed with electrophysiologically defined digit, hand and forelimb representations in area 5?, 3b and 1. Connections with area 3a were observed to be most dense in the hand and forelimb

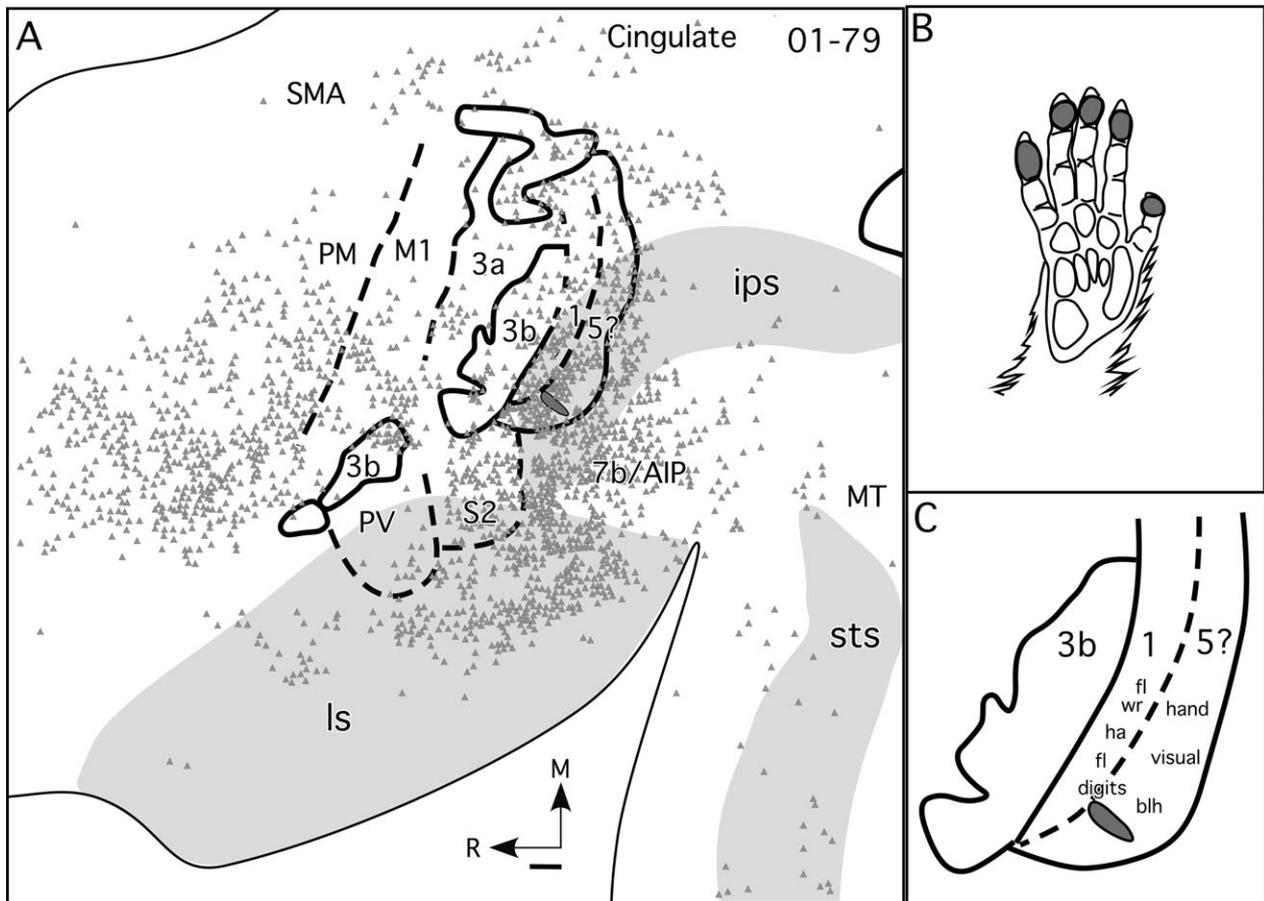


Figure 11. A tangential reconstruction (A) of the ipsilateral connections of area 5? resulting from an injection of FE centered in the representation of the digit tips in case 01-79 (B, C). Connections of area 5? are remarkably similar to those observed in the other two cases illustrated in Figure 10. Conventions as in previous figures.

1971; Merzenich *et al.*, 1978; Sur *et al.*, 1982; Felleman *et al.*, 1983; Carlson *et al.*, 1986; Krubitzer and Kaas, 1990b), prosimian galagos (Sur *et al.*, 1980) and even humans (Penfield and Rasmussen, 1968; Fox *et al.*, 1987; Moore *et al.*, 2000). In all primates investigated, area 3b forms a systematic representation of the contralateral body surface with the tail, genitals and feet represented most medially, followed by the representations of the hindlimb, trunk, forelimb, hand, face and oral structures in a mediolateral progression. A similar type of organization has been described for area 3b in a variety of non-primate mammals including monotremes, marsupials and eutherians (reviewed by Kaas, 1983; Johnson, 1990; Krubitzer, 1995).

The complete topographic organization of area 1 has also been described using electrophysiological recording techniques in the macaque monkey and three species of New World monkeys (macaque: Nelson *et al.*, 1980; owl monkey: Merzenich *et al.*, 1978; squirrel monkey: Sur *et al.*, 1982; cebus monkey: Felleman *et al.*, 1983). In these primates, area 1 forms a mirror reversal representation of area 3b, and neurons in area 1 respond to cutaneous stimulation of the contralateral body surface. In a recent study in titi monkeys (Coq *et al.*, 2004), the lateral portion of area 1 was mapped using electrophysiological

recording techniques similar to those employed in the current investigation. The results from this study were consistent with those in the present investigation as well as with other studies in New World monkeys. Surprisingly, the presence of an area 1 in other primates has not been convincingly demonstrated. For instance, in studies in galagos (Sur *et al.*, 1980; Wu and Kaas, 2003), tamarins (Carlson *et al.*, 1986) and marmosets (Krubitzer and Kaas, 1990b), only a few recording sites were made caudal to area 3b. Those recording sites that contained neurons that were responsive to high-threshold stimulation were often extremely close to the caudal border of area 3b, and may actually have been in the caudal portion of 3b. These previous studies refer to this region as area 1/2 or area 1, but this appears to be based predominantly on location. This lack of secure electrophysiological evidence in support of an area 1 makes the presence of an area 1 in galagos, tamarins and marmosets equivocal.

Ipsilateral cortical connections of area 3b have been described in Old World monkeys (Jones and Wise, 1977; Vogt and Pandya, 1978; Juliano *et al.*, 1990; Darian-Smith *et al.*, 1993; Burton and Fabri, 1995; Burton *et al.*, 1995), New World monkeys (Krubitzer and Kaas, 1990b; Coq *et al.*, 2004) and

representations. Dense connections are also observed with PV, S2, PM, M1, 7b/AIP, LIP/VIP, and cingulate cortex. The maps illustrated in B and E are simplified versions of more extensive mapping illustrated in Figures 2B and 1A respectively. Sparse connections were observed in the STS. Scale bar is 1 mm. Conventions as in previous figures. See Table 3 for abbreviations.

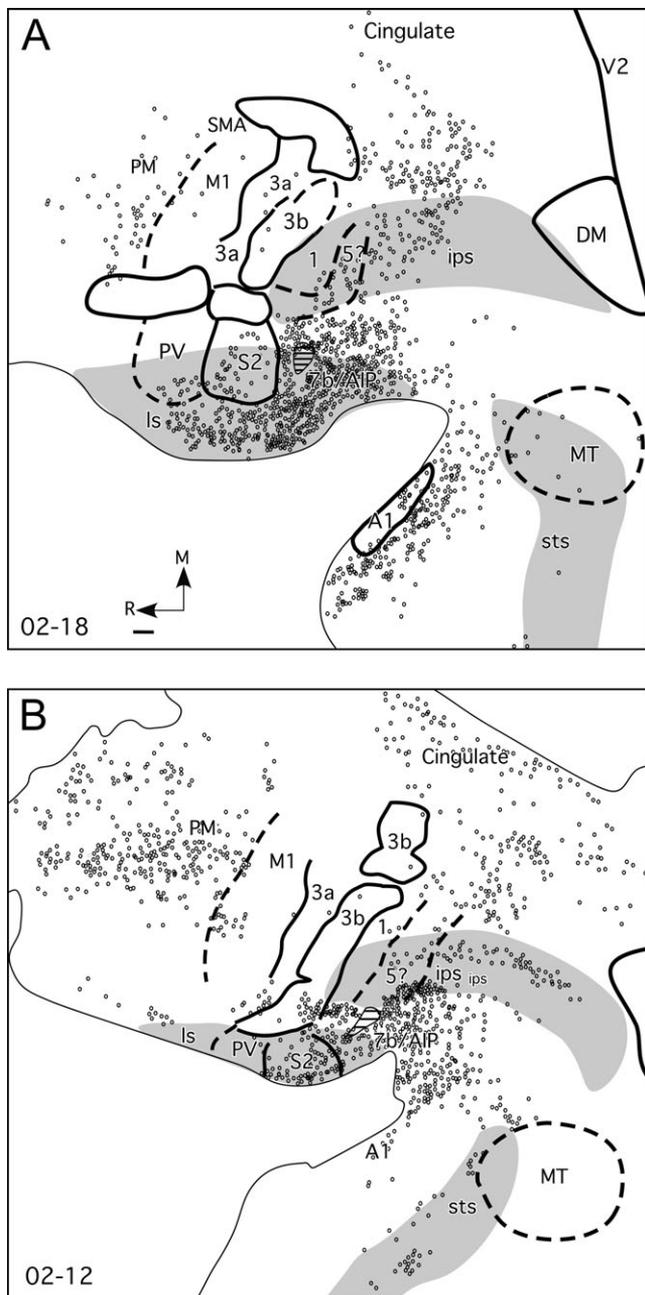


Figure 12. (A) Overall pattern of connections of area 7b/AIP in case 02-18 (A) and 02-12 (B). The pattern of connections of 7b/AIP were remarkably similar for both cases. Connections were observed with the hand, digits and forelimb representation in area 5?, with sparse labeled cells observed in areas 3b and the hand and forelimb representations in 1 (see Fig. 1A). (B) A reconstruction of the ipsilateral connections of area 7b/AIP in case 02-12. In this case, a few labeled cells were observed in area 1, and moderate label was observed in the lateral portion of areas 3b and 3a, in the location of the face representation. Collectively, these injections into area 7b/AIP resulted in dense label in areas 7b/AIP, S2, PV, PM, cortex caudal to area 5? and auditory cortex. Label was also observed in cingulate cortex, and the STS. Scale bar is one millimeter.

prosimian galagos (Wu and Kaas, 2003). In all of these primates, restricted injections in area 3b result in a relatively tight distribution of connections with adjacent somatosensory cortical fields including areas 3a, cortex immediately caudal to area 3b (areas 1 and 2 in macaque monkeys and area 1 in New World monkeys), S2 (and PV where described) and primary motor cortex (Fig. 14). Connections of area 3b reported for the

present investigation are consistent with these previous findings. Highly restricted injections into electrophysiologically identified portions of area 1 have only been made in macaque (Pons and Kaas, 1986; Burton and Fabri, 1995; Burton *et al.*, 1995) and titi monkeys (Coq *et al.*, 2004). Connections of area 1 in these primates were more broadly distributed than those in area 3b and were observed with areas 3b, 2, S2/PV, 5, 7b/AIP and sparsely with areas 3a, M1 and frontal cortex. Interestingly, both the present investigation and the previous study in titi monkeys indicate that the connections of area 1 are more broadly distributed across cortical fields than connections of area 1 in macaque monkeys (Pons and Kaas, 1986; Burton and Fabri, 1995; Burton *et al.*, 1995; Coq *et al.*, 2004).

The role of areas 3b and 1 in sensory processing and ultimately in generating manual behaviors has been investigated predominantly in macaque monkeys using a number of techniques, including single-unit studies in awake monkeys, studies of connections and lesion studies. Together these data indicate that areas 3b and 1 are involved in integrating local inputs from restricted portions of the glabrous hand necessary for texture and hardness discriminations, as well as making discriminations that require movement of the hand, such as discriminating a many-sided object (Randolph and Semmes, 1974; Roland, 1976; LaMotte and Mountcastle, 1979; Carlson, 1981; Chapman and Ageranioti-Belanger, 1991; Sinclair and Burton, 1991; Ageranioti-Belanger and Chapman, 1992; Tremblay *et al.*, 1996; Jiang *et al.*, 1997; Schwartz, 1983).

Do New World Monkeys Have an Area 2?

The most comprehensive data pertaining to cortex caudal to area 1 have been collected in macaque monkeys. Thus, in order to answer the question posed above, a brief review of what is known about the organization and connectivity of fields caudal to area 1 in macaque monkeys is necessary. In macaques, two areas of cortex caudal to area 1 have been clearly delineated: areas 2 and 5. The topographic organization and neural response properties of area 2 have been well described (e.g. Hyvärinen and Poranen, 1978; Pons *et al.*, 1985; Ageranioti-Belanger and Chapman, 1992; Taoka *et al.*, 1998, 2000; Toda and Taoka, 2001, 2002; Iwamura *et al.*, 2002). Neurons in area 2 are highly responsive in the anesthetized and awake animal, and respond to stimulation of cutaneous and deep receptors. Area 2 contains a complete representation of the contralateral body, with a gross mediolateral topography much like that described for areas 3b and 1. Receptive fields for neurons in area 2 are relatively large (sometimes bilateral) when compared to areas 3b and 1 (e.g. Taoka *et al.*, 2000; Iwamura *et al.*, 2002), except for the hand, where receptive fields are predominantly limited to single digits, and individual digits 1 and 2 are represented in an exclusive cortical area. A single study of connections of area 2 in macaques in which injections were placed under electrophysiological guidance indicates that area 2 is mostly connected with other somatosensory cortical areas such as 3b, 1, 3a and S2, as well as with M1 and area 5 (Pons and Kaas, 1986). Although cortex caudal to area 1 has been termed area 2 in squirrel monkeys (Sur *et al.*, 1982), owl monkeys (Merzenich *et al.*, 1978) and titi monkeys (Coq *et al.*, 2004), this region of cortex has either been explored only in a very limited fashion (e.g. Coq *et al.*, 2004) or the data were not illustrated (Merzenich *et al.*, 1978; Sur *et al.*, 1982). The limited data that exist in New World monkeys indicate that neural responsiveness drops off sharply in cortex caudal to area 1, and that neurons respond to joint

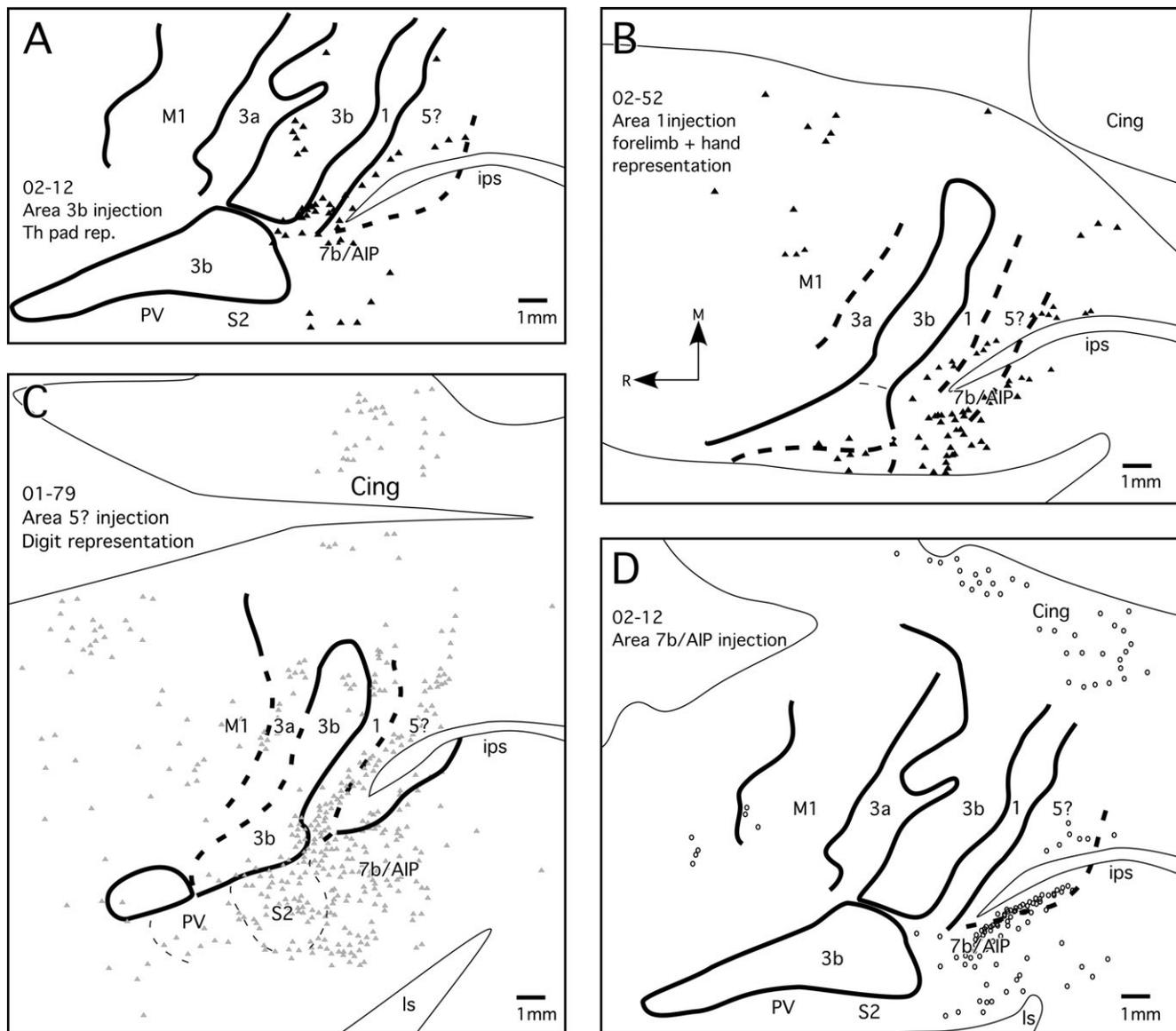


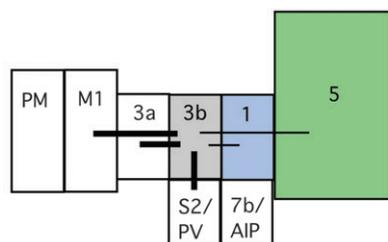
Figure 13. Callosal connections of areas 3b (A), 1 (B), 5? (C) and 7b/AIP (D). (A) Tangential reconstruction of callosal label observed following an injection into the hand plus forelimb representation in area 3b in case 02-12. Sparse label was observed in 3b in the expected location of the forelimb in this case. (B) Callosal label observed following an injection into the hand plus forelimb representation within area 1 in case 02-52. Sparse label was observed in area 1, S2, PV, area 5?, 7b/AIP and premotor cortex in this case. (C) Callosal label observed following an injection into the representation of the hand on the area 1/area 5? border in case 01-79. Labeled cells were observed to be most dense in area 5?, 7b/AIP and S2, and were more sparse in areas 3b and 1. (D) Callosal label observed following an injection into 7b/AIP. Densest label was observed in 7b/AIP and the caudal IPS, and scattered cells were observed in the cingulate and PM.

manipulation, vigorous taps to the body (mostly the hand and forelimb) and in some instances cutaneous stimulation to the hand. These features are more like those of area 5 than area 2 (see below).

Studies of area 5 are also limited to macaque monkeys. Previous studies demonstrate that responsiveness of neurons caudal to area 2 is sharply attenuated in the anesthetized animal (Pons *et al.*, 1985; Disbrow *et al.*, 2001). Neurons that do respond in an anesthetized preparation are activated by cutaneous stimulation of the hand, and by joint manipulation and vigorous taps to the body, predominantly to the forelimb and hand. Studies in anesthetized and awake animals indicate that area 5 is dominated by the representation of the hand and forelimb, and that neurons have large contralateral, ipsilateral and bilateral receptive fields (e.g. Sakata *et al.*, 1973; Mountcastle

et al., 1975; Iwamura *et al.*, 1994, 2002; Taoka *et al.*, 2000; Disbrow *et al.*, 2001; see Iwamura, 2000, for review). Recent studies indicate that neurons in macaque area 5 also respond to visual stimulation (Fig. 15B; Disbrow *et al.*, 2001). There is only one study of area 5 in which electrophysiological guidance was used to place injections (Pons and Kaas, 1986). This previous investigation demonstrated connections with areas 1, 7 (our 7b/AIP), S2, M1 and premotor cortex, which is a subset of the connections of the presumptive area 5 in titi monkeys. Early studies of connections of architectonically defined area 5 to local parietal cortical areas support the more recent study by Pons and colleagues (e.g. Jones and Powell, 1969; Jones *et al.*, 1978; Pandya and Seltzer, 1982). Thus connections of area 5 in the macaque are widespread compared to anterior parietal fields.

Connections of area 3b



Connections of area 5

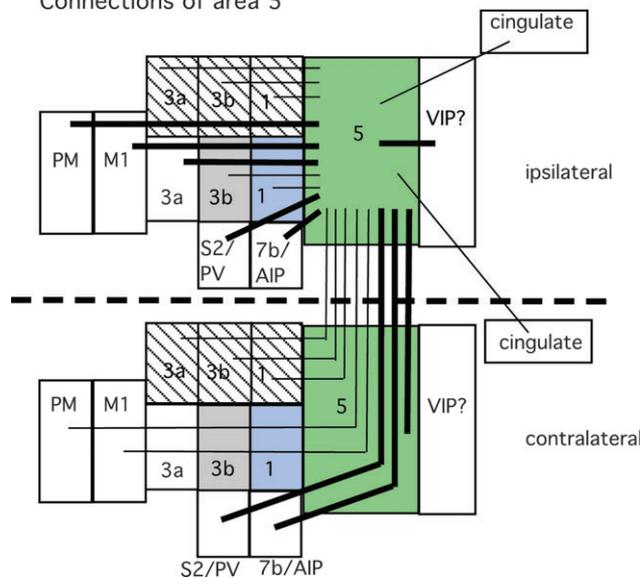


Figure 14. Comparison of connection patterns of the hand representation of areas 3b and 5? in titi monkeys. The hand representation of area 3b (gray) has a highly restricted pattern of connections with the hand representation of areas 3a, 1 (blue) and M1. Dense connections are also with S2 and PV and sparse connections are with area 5? (green). There are no connections with the opposite hemisphere. Connections of area 5? are much more widespread both within and across hemispheres. Dense connections are observed with extrastriate visual cortex (VIP?), motor and premotor cortex, S2, PV and 7b/AIP. Moderate connections are observed with similar body part representations in areas 3b, 1 and 3a, as well as with other mismatched body part representations (lines). Moderate ipsilateral connections are also with cingulate cortex. Dense contralateral connections are observed with the hand representation of area 5? in the opposite hemisphere, with S2, PV and AIP. Moderate connections are observed with motor areas of the neocortex as well as with mismatched body part representations in areas 3a, 3b and 1. The thick dashed line below the middle figure represents the midline of the brain.

In the current investigation we identified a field immediately caudal to area 1 that we termed the presumptive area 5. We believe this field in the titi monkey is homologous to area 5 rather than to area 2 in macaque monkey for several reasons. First, neurons in our presumptive area 5 are less well driven in an anesthetized preparation, similar to neurons in macaque area 5 but not area 2 (Pons *et al.*, 1985). On the contrary, neurons in area 2, under similar recording conditions, can be readily driven, receptive fields defined and topographic maps generated. Thus, lack of a vigorous response in an anesthetized preparation is a characteristic of area 5, rather than area 2. Second, the field we term area 5? in titi monkeys is dominated by the representation of the hand and forelimb, as is area 5 in macaque monkeys (Fig. 15). Third, receptive fields in area 5? generally encompass the entire hand or all digits, a feature of area 5, but not of area 2. Fourth, neurons in our presumptive area 5 were also driven by visual stimulation, as in macaque area 5 (Fig. 15). Fifth, the

connections of our presumptive area 5 are more like those described for area 5 in macaque monkeys than like area 2. For example, connections of area 5 in both titi and macaque monkeys are broadly distributed and are more dense with motor, premotor and extrastriate visual areas of the cortex than with somatosensory areas. As noted above, area 2 in macaque monkeys is connected most densely with other somatosensory areas. Finally, the architectonic appearance of our area 5? is like that of area 5 in macaque monkeys rather than area 2. Thus, in titi monkeys cortex caudal to area 1 is organized quite differently than that described for area 2 in macaque monkeys.

It is interesting that in the comprehensive comparative survey of cortical cytoarchitecture of Brodmann (1909), he distinguishes an area 5 in Old World macaque monkeys as well as in New World marmosets, monkeys and lemurs. However, in the macaque monkey, area 5 resides immediately caudal to area 2, while in marmoset monkeys and lemurs, area 5 resides immediately caudal to what Brodmann terms areas 1-3 and 1 respectively. In non-primate mammals such as flying foxes, ground squirrels and hedgehogs, Brodmann also distinguishes an area 5. Its location relative to areas 3 and 1 varies in these species, but a consistent observation is that no area 2 was observed in these mammals or in non-anthropoid primates. We believe the data from the present and previous studies indicates that, unlike Old World monkeys, New World monkeys do not have an area 2.

Presumptive Areas 7b/AIP in Titi Monkeys

In the present investigation, cortex caudolateral to the presumptive area 5 was termed area 7b/AIP based on location and similarities in connections with these fields described in macaque monkeys, as well as the prosimian galago. Previous studies in macaque monkeys demonstrate that area 7b resides mostly on the upper bank of the lateral sulcus, just caudal to S2, and spreads onto the inferior parietal lobule, just lateral to the rostral tip of the IPS (e.g. Robinson and Burton, 1980; Krubitzer *et al.*, 1995). Single and multi-unit studies in macaque monkeys demonstrate that receptive fields of neurons in area 7b are large and directionally selective and are active during movements of the arms (Hyvärinen and Poranen, 1974; Hyvärinen and Shelpin, 1979; Leinonen *et al.*, 1979; Hyvärinen, 1982; Krubitzer *et al.*, 1995). The anterior intraparietal area (AIP) has been described in macaque monkeys as a cortical field residing at the anterior tip of the IPS in which neurons respond to visually guided hand manipulations (Sakata *et al.*, 1995; see Cavada, 2001; Andersen and Buneo, 2002, for review). Neurons in AIP are responsive to visual stimulation and are selective for object shape (Murata *et al.*, 2000).

Only a few studies have examined the connections of areas 7b (Neal *et al.*, 1986, 1987, 1990; Cavada and Goldman-Rakic, 1989a,b; Andersen *et al.*, 1990; Lewis and Van Essen, 2000; Wu and Kaas, 2003; see also Guldin *et al.*, 1992, who termed this 7 anterior) and AIP (Lewis and Van Essen, 2000; Nakamura *et al.*, 2001). Area 7b has connections with S2 (or areas in the lateral sulcus), area 5 (or cortex in the rostral and caudal bank of the lateral IPS), with VIP, cingulate cortex, STS cortex, divisions of premotor cortex and orbital cortex. AIP has connections with areas 7, LIP, MIP, VIP, 5 (or 5V), S2 and with regions of premotor cortex (Lewis and Van Essen, 2000; Nakamura *et al.*, 2001). However, injections in these studies were not restricted to AIP and may have incorporated other fields such as area 7b. The connections of area 7b and AIP are remarkably similar in the

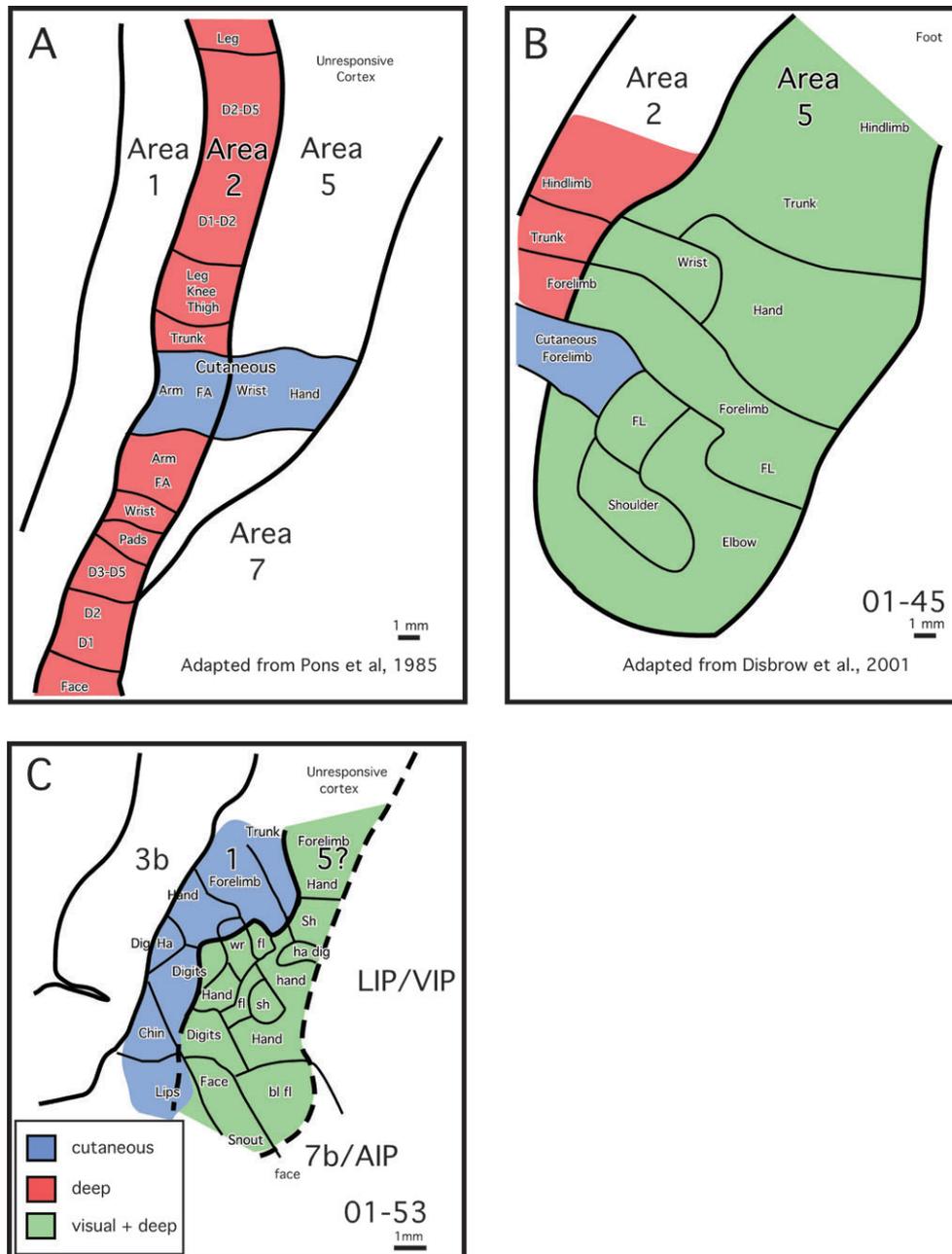


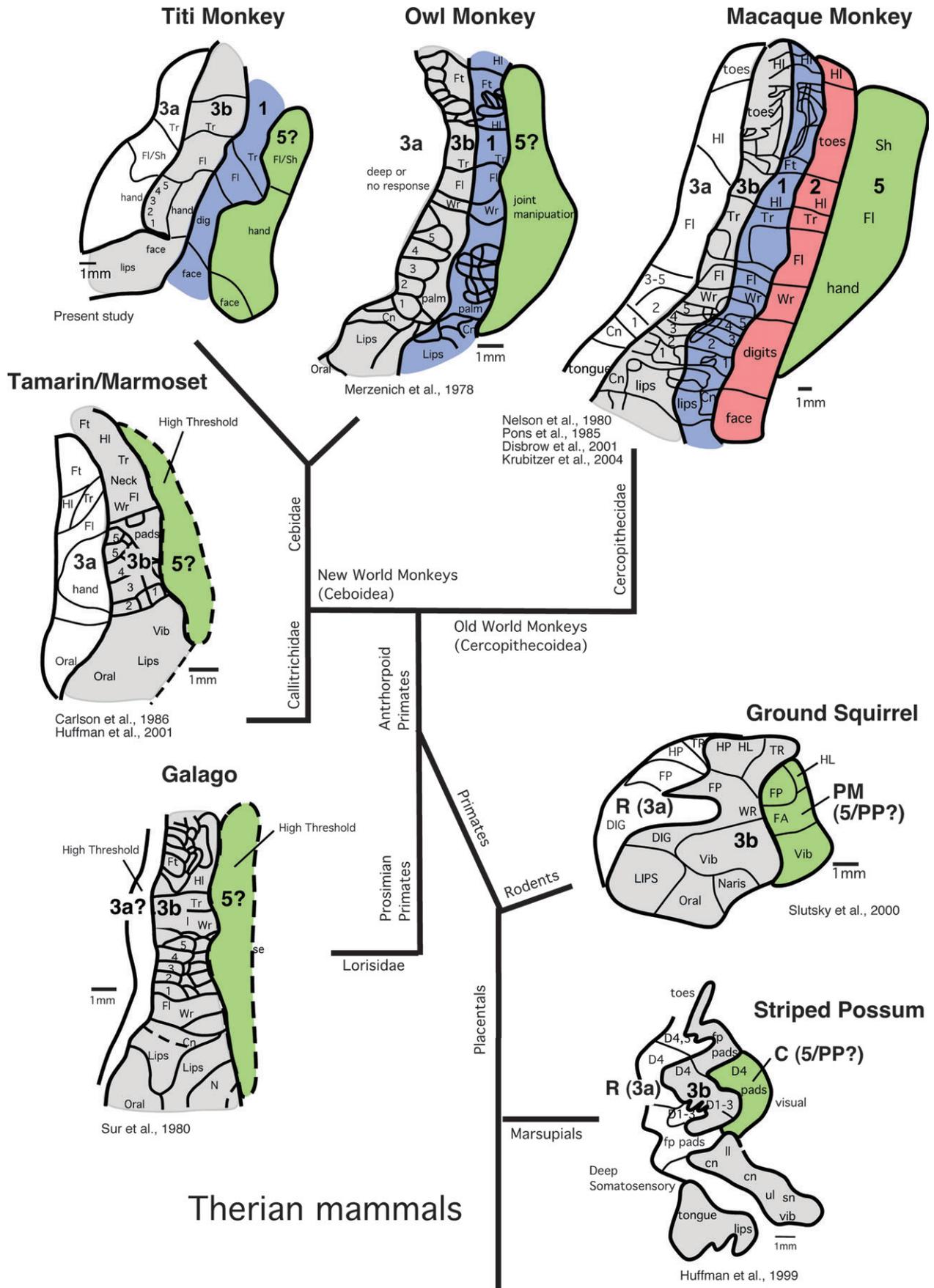
Figure 15. Comparison of areas 2 and 5 in macaque monkeys with the presumptive in titi monkeys. (A) Summary of an electrophysiological map adapted from Pons *et al.* (1985). In this study, most neurons within area 2 responded to stimulation of deep receptors. A zone of cortex containing neurons responsive to cutaneous somatosensory stimulation was observed bridging areas 2 and 5. (B) Summary of an electrophysiological map adapted from Disbrow *et al.* (2000). As in the study shown in panel A, area 2 was observed to contain neurons that responded to stimulation of deep receptors, and a zone of cortex containing neurons that responded to cutaneous somatosensory stimulation was observed within both areas 2 and 5. Neurons across a large extent of area 5 were observed to respond to stimulation of deep receptors of the hand and forelimb. Additionally, many of the sites surveyed in area 5 were observed to contain neurons that responded to both deep somatosensory and visual stimulation. (C) Summary electrophysiological map from the current study. Note that the cortical field directly caudal to area 1 in titi monkeys had a large portion of cortex which contained neurons that responded to stimulation deep receptors of the hand and forelimb, and that many of these neurons responded to both deep somatosensory and visual stimulation. These characteristics suggest that cortex directly caudal to area 1 in titi monkeys is more like area 5 rather than area 2 of macaque monkeys, and we have therefore termed this field the presumptive area 5.

macaque and one wonders if these regions are indeed two distinct subdivisions. In the present investigation in titi monkeys, cortex in the relative location of areas 7b and AIP contained neurons that responded to visual stimulation (in two cases), although no attempt was made to map receptive fields. Injections in this area revealed a similar pattern of connectivity to that described above for area 7b as well as that described for AIP.

Callosal Connections of Anterior and Posterior Parietal Areas

Areas 3b and 1

Callosal connections of areas 3b, 1 and 2 have collectively been described for primates (e.g. Pandya and Vignolo, 1968; Jones *et al.*, 1979; Killackey *et al.*, 1983; Shanks *et al.*, 1985). All of these studies report that the hand representations in areas 3b



and 1 are acallosal. Surprisingly, specific callosal connections of electrophysiologically defined anterior parietal fields have only been described for area 3b in marmoset monkeys (Krubitzer and Kaas, 1990b). In marmosets, callosal connections of area 3b are differentially distributed within this field. Myelin-light portions of area 3b are strongly interconnected, while myelin-dense portions of 3b are acallosal. Further, the hand representation of area 3b appears to be mostly acallosal. The results of the present study are similar to those described previously in marmosets in that only the injection in the lateral portion of the hand representation in 3b in titi monkeys, which incorporated the myelin-light callosal zone, resulted in connections in the opposite hemisphere. In this case, only a few labeled cells were observed in area 3b medial to the expected location of the hand representation, and in areas 1, 5? and 7b/AIP (Fig. 13A).

Like area 3b, no callosal connections were observed in the present investigation in the two cases in which the hand and digit representations in area 1 were injected. However, callosal connections were observed for the injections that included portions of the forelimb representation in area 1, particularly with areas 5? and 7b/AIP. Thus, in areas 3b and 1 there appear to be discrete callosal zones related to myelin-light regions, and/or different body part representations. This type of organization may be a general feature of mammalian cortex since similar callosal zones have been observed in flying foxes (Krubitzer *et al.*, 1998), rats (Akers and Killackey, 1978) and other primates (see Krubitzer *et al.*, 1998, for review).

The Presumptive Areas 5 and 7b/AIP

Studies of callosal connectivity of posterior parietal cortex have examined total patterns of connections of large regions of cortex (e.g. Karol and Pandya, 1971; Killackey *et al.*, 1983), or connections of several fields grouped together such as 3a, 3b, 1, 2 and 5 collectively (e.g. Jones and Powell, 1969; Boyd *et al.*, 1971; Jones *et al.*, 1975, 1979; Shanks *et al.*, 1985). A consistent observation among these studies is that area 5 receives dense callosal inputs throughout the field (i.e. including the hand representation). One study in which the connections of cortex in the location of area 5 was examined (Caminiti and Sbriccoli, 1985) noted that callosal connections were found throughout area 5, the supplementary motor area, 7b, and with the dorsal bank of the lateral sulcus (in the S2/PV region). Our studies in titi monkeys indicate that the hand representation of the presumptive area 5 has dense callosal connections with the contralateral area 5? as well as 7b/AIP, S2/PV (Fig. 14), a finding similar to that of Caminiti and Sbriccoli (1985).

There are several studies in which callosal connectivity of area 7b, or cortex in the location of areas 7b and AIP, was examined (Pandya and Vignolo, 1968; Jones and Powell, 1969; Neal, 1990). The pattern of callosal connections was similar to that described for area 7b/AIP in the present study in titi

monkeys, in that transported tracer or axonal degeneration was observed predominantly in 7b/AIP in the opposite hemisphere.

Taken together, these results indicate that area 5 is one of the few somatosensory cortical areas involved in integrating inputs between the hands. Such connections could form the substrate for interhemispheric transfer of information necessary for bilateral limb and hand coordination.

The Evolution of Anterior and Posterior Parietal Cortex in Primates

Anterior Parietal Cortex

The presence of an area 1 or a rudimentary area 1 in several New World primates and macaque monkeys, and the apparent absence of area 1 in marmosets, tamarins and prosimian galagos suggest two possible scenarios regarding the evolution of area 1. The first is that area 1 evolved early in primate evolution in a primitive form and was lost in both prosimians and New World Callitrichidae. The second is that area 1 arose after the divergence of anthropoid and prosimian primates and was lost in at least one lineage, Callitrichidae (Fig. 16), was retained in a primitive form in some species such as titi monkeys, and became well developed in other species such as cebus, squirrel and macaque monkeys, possibly with the evolution of the hand. It should be noted that the two species of New World monkeys (tamarins and marmosets) which do not possess an area 1 have a modified hand with claws specialized for climbing rather than object discrimination and manipulation.

The functional organization of area 2 has only been described in one species of non-human primates, the macaque monkey (Pons *et al.*, 1985), and has recently been identified in humans (Moore *et al.*, 2000). Results from the present investigation as well as previous studies in New World monkeys suggest that these primates do not possess an area 2. It is possible that area 2 arose, or co-evolved with the emergence of an opposable thumb, and is related to the behaviors associated with using a variety of grips for tactile exploration and identification. This notion is supported by observation that the digits, hand and forelimb representations in area 2 are magnified, more so than in areas 3b and 1, and that area 2 is densely interconnected with posterior parietal areas associated with hand use, such as area 5. Regardless of the status of area 2 in various primates, it is important to note that comparisons of neocortical organization across primates and across mammals suggest that unimodal somatosensory cortical areas, such as areas 1 and 2, appear to have emerged solely in the primate order (Fig. 16), possibly in relation to sophisticated manual abilities.

Posterior Parietal Cortex

In non-primate mammals, such as squirrels (e.g. Fig. 16; Slutsky *et al.*, 2000), insectivores (Krubitzer *et al.*, 1997), some marsupials (Beck *et al.*, 1996; Huffman *et al.*, 1999; Frost

Figure 16. A simplified cladogram depicting the phylogenetic relationship of primates and other mammals, and the organization of anterior and posterior parietal cortex in several species. Comparative data from these and other mammals indicate that early therian mammals possessed a primary somatosensory area (3b or S1, light gray), a rostral field (3a or R, white), and a caudal area (5 or PP, green). Some species such as simian primates have evolved a low threshold cutaneous (or deep) representation just caudal to 3b, termed area 1 (blue). Since area 1 has not been identified in other mammals, or even in prosimian primates, it is likely that area 1 evolved after the simian and prosimian divergence. Area 2 (orange) has only been identified in macaque monkeys. Comparisons across mammals indicate that areas 3a, 3b and 5 are evolutionarily old fields, and that new, unimodal somatosensory fields such as areas 1 and 2 evolved later in some lineages, and are interspersed between existing fields (i.e. are not added hierarchically). We propose that areas 1 and 2 evolved with the modified morphology of the hand in anthropoid primates, and that older, retained fields, such as area 5, were modified both functionally and connectionally for sophisticated hand use. Phylogenetic relationships come from Murphy *et al.* (2001) and Eisenberg (1981). Cortical organization of different species depicted here is modified from studies listed for each species.

et al., 2000) and the flying fox (Krubitzer and Calford, 1992), cortex immediately caudal to area 3b contains neurons that respond to stimulation of deep receptors of the contralateral body and often to visual stimulation. This field has been termed the caudal field, C, the caudal somatosensory area, SC, the parietal medial area, PM, or area 1/2 (and LP). In most non-primate mammals in which this region of cortex has been mapped extensively, this cortical area is dominated by the representation of a particular, behaviorally relevant body part or a few body parts such as the forepaw, forelimb and vibrissae of squirrels, D1 of flying foxes or D4 of striped possums (Fig. 16).

Although cortex immediately caudal to 3b in non-primate mammals has traditionally often been considered to be the homolog of primate area 1, the only evidence for this view is that this presumptive area 1 is immediately caudal to area 3b. It should be noted that in a number of species examined, not only is this area immediately caudal to area 3b, but it is immediately rostral to V2, which would make it V3 if one were to assume homology based solely on relative location. However, if one considers the extreme magnification of particular body parts, the presence of neurons that often respond to visual stimulation as well as stimulation of deep receptors, the relative location of this field with respect to 3b and visual cortex, and the fact that it has dense callosal connections, then this field is more like posterior parietal cortex (area 5) than like areas 1 or 2.

The presence of an area 5 in both New World and Old World monkeys, and a rudimentary form of posterior parietal cortex in most mammals studied suggests that this cortex arose early in evolution and has been retained in most or all mammals (Fig. 16). While this region of cortex may be a homologous cortical area in all mammals, the addition of new areas, such as 1 and 2, and new connections probably promotes new functions of this area in primates.

Taken together we believe the data indicate that in primates, unimodal somatosensory cortex has expanded with the addition of areas 1 and 2, and that area 5 underwent a number of changes in primates including a magnification of the hand and forelimb representation, the preponderance of neurons active under different reaching and grasping paradigms, and the broad distribution of ipsilateral and contralateral connections of the hand and limb representation with proprioceptive, limbic and motor cortex (Fig. 14). All of these features are coincident with the evolution of the hand and opposable thumb in a number of primates, as well as with a larger repertoire of grips and manual and bimanual hand configurations (Napier, 1960, 1969; Welles, 1976; Marzke and Marzke, 2000).

Notes

We would like to dedicate this manuscript to the late Dr. Tim Pons, a friend, colleague, and a wonderful scientist.

We wish to thank Gregg Recanzone, Dianna Kahn, Deborah Hunt and Sarah Long for helpful comments on this manuscript. This work was supported by an NINDS grant to Leah Krubitzer (RO1 NS35103-07) and an NEI grant to Jeffrey Padberg (F32 EY014503-01A1).

Address correspondence to Leah Krubitzer, Center for Neuroscience, 1544 Newton Ct, Davis, CA 95616, USA. Email: lakrubitzer@ucdavis.edu.

References

Ageranioti-Belanger SA, Chapman CE (1992) Discharge properties of neurones in the hand area of primary somatosensory cortex in monkeys in relation to the performance of an active tactile

- discrimination task. II. Area 2 as compared to areas 3b and 1. *Exp Brain Res* 91:207-228.
- Akers RM, Killackey HP (1978) Organization of corticocortical connections in the parietal cortex of the rat. *J Comp Neurol* 181:513-537.
- Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. *Annu Rev Neurosci* 25:189-220.
- Andersen RA, Asanuma C, Essick G, Siegel RM (1990) Corticocortical connections of anatomically and physiologically defined subdivisions within the inferior parietal lobule. *J Comp Neurol* 296:65-113.
- Beck PD, Pospichal MW, Kaas JH (1996) Topography, architecture, and connections of somatosensory cortex in opossums: evidence for five somatosensory areas. *J Comp Neurol* 366:109-133.
- Boyd EH, Pandya DN, Bignall KE (1971) Homotopic and nonhomotopic interhemispheric cortical projections in the squirrel monkey. *Exp Neurol* 32:256-274.
- Brodmann K (1909) Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien Dargestellt auf Grund des Zellenbaues. Leipzig: Barth.
- Burbaud P, Doegle C, Gross C, Bioulac B (1991) A quantitative study of neuronal discharge in areas 5, 2 and 4 of the monkey during fast arm movements. *J Neurophysiol* 66:429-443.
- Burton H, Fabri M (1995) Ipsilateral intracortical connections of physiologically defined cutaneous representations in areas 3b and 1 of macaque monkeys: projections in the vicinity of the central sulcus. *J Comp Neurol* 355:508-538.
- Burton H, Fabri M, Alloway K (1995) Cortical areas within the lateral sulcus connected to cutaneous representations in areas 3b and 1: a revised interpretation of the second somatosensory area in macaque monkeys. *J Comp Neurol* 355:539-562.
- Caminiti R, Sbriccoli A (1985) The callosal system of the superior parietal lobule in the monkey. *J Comp Neurol* 2237:85-99.
- Carlson M (1981) Characteristics of sensory deficits following lesions of Brodmann's areas 1 and 2 in the postcentral gyrus of *Macaca mulatta*. *Brain Res* 204:424-430.
- Carlson M, Huerta MF, Cusick CG, Kaas JH (1986) Studies on the evolution of multiple somatosensory representations in primates: the organization of anterior parietal cortex in the New World Callitrichid, *Saguinus*. *J Comp Neurol* 246:409-426.
- Cavada C (2001) The visual parietal areas in the macaque monkey: current structural knowledge and ignorance. *Neuroimage* 14:S21-S26.
- Cavada C, Goldman-Rakic PS (1989a) Posterior parietal cortex in rhesus monkey: I. Parcellation of areas based on distinctive limbic and sensory corticocortical connections. *J Comp Neurol* 287:393-421.
- Cavada C, Goldman-Rakic PS (1989b) Posterior parietal cortex in rhesus monkey: II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. *J Comp Neurol* 287:422-445.
- Chapman CE and Ageranioti-Belanger SA (1991) Discharge properties of neurones in the hand area of primary somatosensory cortex in monkeys in relation to the performance of an active tactile discrimination task. I. Areas 3b and 1. *Exp Brain Res* 87:319-339.
- Chen LM, Friedman RM, Ramsden BM, LaMotte RH, Roe AW (2001) Fine-scale organization of S1 (area 3b) in the squirrel monkey revealed with intrinsic optical imaging. *J Neurophysiol* 86:3011-3029.
- Coq J-O, Huixin QI, Collins CE, Kaas JH (2004) Anatomical and functional organization of somatosensory areas of the lateral fissure of the New World monkey (*Callicebus moloch*). *J Comp Neurol* 476:363-387.
- Darian-Smith C, Darian-Smith I, Burman K, Ratcliffe N (1993) Ipsilateral cortical projections to areas 3a, 3b, and 4 in the macaque monkey. *J Comp Neurol* 335:200-213.
- Debowy DJ, Ghosh S, Ro JY, Gardner EP (2001) Comparison on neuronal firing rates in somatosensory and posterior parietal cortex during prehension. *Exp Brain Res* 137:269-291.
- Disbrow EA, Huffman KJ, Recanzone G, Krubitzer LA (2000) The connections of areas 5 and 2 with electrophysiologically identified somatosensory cortical areas in macaque monkeys. *Soc Neurosci Abstr* 26:2082.

- Disbrow EA, Murray SO, Roberts TP, Litinas ED, Krubitzer LA (2001) Sensory integration in human posterior parietal area 5. *Soc Neurosci Abstr* 27:511-526.
- Disbrow E, Litinas E, Recanzone G, Padberg J, Krubitzer L (2003) Cortical connections of the parietal ventral area and the second somatosensory area in macaque monkeys. *J Comp Neurol* 462:382-399.
- Eisenberg (1981) *The mammalian radiations: an analysis of trends in evolution, adaptation and behavior*. New York: Continuum.
- Felleman DJ, Nelson RJ, Sur M, Kaas JH (1983) Representations of the body surface in areas 3b and 1 of postcentral parietal cortex of cebus monkeys. *Brain Res* 268:15-26.
- Ferraina S, Bianchi L (1994) Posterior parietal cortex: Functional properties of neurons in area 5 during an instructed-delay reaching task within different parts of space. *Exp Brain Res* 99:175-178.
- Fox PT, Burton H, Raichle ME (1987) Mapping human somatosensory cortex with positron emission tomography. *J Neurosurg* 67:34-43.
- Frost SB, Milliken GW, Plautz EJ, Masterton RB, Nudo RJ (2000) Somatosensory and motor representations in cerebral cortex of a primitive mammal (*Monodelphis domestica*): a window into the early evolution of sensorimotor cortex. *J Comp Neurol* 421:29-51.
- Gallyas F (1979) Silver staining of myelin by means of physical development. *Neurology* 1:203-209.
- Gardner E (1988) Somatosensory cortical mechanisms of feature detection in tactile and kinesthetic discrimination. *Can J Physiol Pharmacol* 66:439-454.
- Graziano MSA, Cooke DF, Taylor CSR (2000) Coding the location of the arm by sight. *Science* 290:1782-1786.
- Guldin WO, Akbarian S, Grusser OJ. (1992) Cortico-cortical connections and cytoarchitectonics of the primate vestibular cortex: a study in squirrel monkeys (*Saimiri sciureus*). *J Comp Neurol* 326:375-401.
- Hill, W (1966) *Primates*, vol. VI. New York: Interscience.
- Huffman KJ, Krubitzer L (2001) Area 3a: topographic organization and cortical connections in marmoset monkeys. *Cereb Cortex* 11:849-867.
- Huffman K, Nelson J, Clarey J, Krubitzer L (1999) Organization of somatosensory cortex in three species of marsupials, *Dasyurus hallucatus*, *Dactylopsila trivirgata*, and *Monodelphis domestica*: neural correlates of morphological specializations. *J Comp Neurol* 403:5-32.
- Hyvärinen J (1982) Posterior parietal lobe of the primate brain. *Physiol Rev* 62:1060-1129.
- Hyvärinen J, Poranen A (1974) Function of the parietal associative area 7 as revealed from cellular discharges in alert monkeys. *Brain* 97:673-692.
- Hyvärinen J, Poranen A (1978) Receptive field integration and sub-modality convergence in the hand area of the post-central gyrus of the alert monkey. *J Physiol* 283:539-556.
- Hyvärinen J, Shelpin Y (1979) Distribution of visual and somatic functions in the parietal associative area 7 of the monkey. *Brain Res* 169:561-564.
- Iriki A, Tanaka M, Iwamura Y (1996) Coding of modified body schema during tool use by macaque postcentral neurons. *Neuroreport* 7:2325-2330.
- Iriki A, Tanaka M, Obayashi S, Iwamura Y (2001) Self-images in the video monitor coded by monkey intraparietal neurons. *Neurosci Res* 40:163-173.
- Iwamura Y (2000) Bilateral receptive field neurons and callosal connections in the somatosensory cortex. *Phil Trans R Soc Lond B* 355:267-273.
- Iwamura Y, Iriki A, Tanaka M. (1994) Bilateral hand representation in the postcentral somatosensory cortex. *Nature* 369:554-556.
- Iwamura Y, Tanaka M, Iriki A, Taoka M, Toda T, (2002) Processing of tactile and kinesthetic signals from bilateral sides of the body in the postcentral gyrus of awake monkeys. *Behav Brain Res* 135:185-190.
- Jain N, Qi HX, Catania KC, Kaas JH (2001) Anatomic correlates of the face and oral cavity representations in the somatosensory cortical area 3b of monkeys. *J Comp Neurol* 429:455-468.
- Jiang W, Tremblay F, Chapman CE. (1997) Neuronal encoding of texture changes in the primary and the secondary somatosensory cortical areas of monkeys during passive texture discrimination. *J Neurophysiology* 77:1656-1662.
- Johnson JI (1990) Comparative development of somatic sensory cortex. In: *Cerebral cortex* (Jones EG, Peters A, eds), pp. 335-449. New York: Plenum.
- Jones EG, Powell TPS (1969) Connexions of the somatic sensory cortex of the rhesus monkey II contralateral cortical connexions. *Brain* 92:717-730.
- Jones EG, Wise SP (1977) Size, laminar and columnar distribution of efferent cells in the sensory-motor cortex of monkeys. *J Comp Neurol* 175:391-438.
- Jones EG, Burton H, Porter R (1975) Commissural and cortico-cortical 'columns' in the somatic sensory cortex of primates. *Science* 190:572-574.
- Jones EG, Coulter JD, Hendry SHC (1978) Intracortical connectivity of architectonic fields in the somatic sensory, motor and parietal cortex of monkeys. *J Comp Neurol* 181:291-348.
- Jones E, Coulter J, Wise S (1979) Commissural columns in the sensory-motor cortex of monkeys. *J Comp Neurol* 188:113-136.
- Juliano S, Friedman D, Eslin D (1990) Corticocortical connections predict patches of stimulus-evoked metabolic activity in monkey somatosensory cortex. *J Comp Neurol* 298:23-39.
- Kaas JH (1983) What, if anything, is SI? Organization of first somatosensory area of cortex. *Physiol Rev* 63:206-230.
- Kalaska JF, Scott SH, Cisek P, Sergio LE (1997) Cortical control of reaching movements. *Curr Opin Neurobiol* 7:849-859.
- Karol EA, Pandya DN (1971) The distribution of the corpus callosum in the rhesus monkey. *Brain* 94:471-786.
- Killackey HP, Gould HJ, Cusick CG, Pons TP, Kaas JH (1983) The relation of corpus callosum connections to architectonic fields and body surface maps in sensorymotor cortex of new and old world monkeys. *J Comp Neurol* 219:384-419.
- Krubitzer L (1995) The organization of neocortex in mammals: are species differences really so different? *Trends Neurosci* 18:408-417.
- Krubitzer LA, Kaas JH (1990a). Cortical connections of MT in four species of primates: Areal, modular, and retinotopic patterns. *Vis Neurosci* 5:165-204.
- Krubitzer LA, Kaas JH (1990b) The organization and connections of somatosensory cortex in marmosets. *J Neurosci* 10:952-974.
- Krubitzer LA, Calford MB (1992) Five topographically organized fields in the somatosensory cortex of the flying fox: microelectrode maps, myeloarchitecture, and cortical modules. *J Comp Neurol* 317:1-30.
- Krubitzer L, Disbrow E (2004) The evolution of parietal areas involved in hand use in primates. In: *Spatial perception*. Cambridge: Cambridge University Press (in press).
- Krubitzer L, Clarey J, Tweedale R, Elston G, Calford M. (1995) A redefinition of somatosensory areas in the lateral sulcus of macaque monkeys. *J Neurosci* 15:3821-3839.
- Krubitzer L, Künzle H, Kaas J (1997) Organization of sensory cortex in a madagascan insectivore, the tenrec (*Echinops telfairi*). *J Comp Neurol* 379:399-414.
- Krubitzer L, Clarey J, Tweedale J, Calford M (1998) Interhemispheric connections of somatosensory cortex in the flying fox. *J Comp Neurol* 402:538-559.
- Krubitzer L, Huffman KJ, Disbrow E, Recanzone G (2004) Organization of area 3a in macaque monkeys: contributions to the cortical phenotype. *J Comp Neurol* 471:97-111.
- Lacquaniti F, Guigon E, Bianchi L, Ferraina S, Caminiti R (1995) Representing spatial information for limb movement: the role of area 5 in monkey. *Cereb Cortex* 5:391-409.
- LaMotte RH, Mountcastle VB (1979) Disorders in somesthesia following lesions in parietal lobe. *J Neurophysiol* 42:400-419.
- Leinonen L, Hyvärinen J, Nyman G, Linnankoski I (1979) I. Functional properties of neurons in lateral part of associative area 7 in awake monkeys. *Exp Brain Res* 34:299-320.
- Lewis J, Van Essen D (2000) Corticocortical connections of visual sensorimotor, multimodal processing areas in the parietal lobe of the macaque monkey. *J Comp Neurol* 428:112-137.
- Luethke LE, Krubitzer LA, Kaas JH (1989) Connections of primary auditory cortex in the New World monkey, *Saguinus*. *J Comp Neurol* 285:487-513.

- Marzke MW, Marzke RF (2000) Evolution of the human hand: approaches to acquiring analyzing and interpreting anatomical evidence. *J Anat* 197:121-140.
- Merzenich MM, Kaas JH, Sur M, Lin C-S (1978) Double representation of the body surface within cytoarchitectonic areas 3b and 1 in 'SI' in the owl monkey (*Aotus trivirgatus*). *J Comp Neurol* 181:41-74.
- Moore C, Stern C, Corkin S, Fischl B, Gray A, Rosen B, Dale A (2000) Segregation of somatosensory activation in the human Rolandic cortex using fMRI. *J Neurophysiol* 84:558-569.
- Mountcastle VB, Lynch JC, Georgopoulos A, Sakata H, Acuna C (1975) Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *J Neurophysiol* 38:871-908.
- Murata A, Gallese V, Luppino G, Kaseda M, Sakata H (2000) Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. *J Neurophysiol* 83:2580-2601.
- Murphy WJ, Eizirik E, O'Brien SJ, Madsen O, Scally M, Douady CJ, Teeling E, Ryder OA, Stanhope MJ, de Jong WW, Springer MS (2001) Resolution of the early placental mammal radiation using Bayesian phylogenetics. *Science* 294:2348-2351.
- Nakamura H, Kuroda T, Wakita M, Kusunoki M, Kato A, Mikami A, Sakata H, Itoh K. (2001) From three-dimensional space vision to prehensile hand movements: the lateral intraparietal area links the area V3A and the anterior intraparietal area in macaque monkeys. *J Neurosci* 21:8174-8187.
- Napier JR (1960) Studies of the hands of living primates. *Proc Zool Soc Lond* 134:647-657.
- Napier J (1962) The evolution of the hand. *Scient Am* 207:56-61.
- Neal JW (1990) The callosal connections of area 7b, PF in the monkey. *Brain Res* 514:159-62.
- Neal JW, Pearson RC, Powell TP (1986) The organization of the corticocortical projection of area 5 upon area 7 in the parietal lobe of the monkey. *Brain Res* 381:164-167.
- Neal JW, Pearson RC, Powell TP (1987) The cortico-cortical connections of area 7b, PF, in the parietal lobe of the monkey. *Brain Res* 419:341-346.
- Neal JW, Pearson RCA, Powell TPS (1990) The ipsilateral cortico-cortical connections of 7b, PF, in the parietal and temporal lobes of the monkey. *Brain Res* 524:119-132.
- Nelson RJ, Sur M, Felleman DJ, Kaas JH (1980) Representations of the body surface in postcentral parietal cortex of *Macaca fascicularis*. *J Comp Neurol* 192:611-643.
- Pandya DN, Seltzer B (1982) Intrinsic connections and architectonics of posterior parietal cortex in the rhesus monkey. *J Comp Neurol* 204:196-210.
- Pandya DN, Vignolo LA (1968) Interhemispheric neocortical projections of somatosensory areas I and II in the rhesus monkey. *Brain Res* 7:300-303.
- Penfield W, Rasmussen T (1968) Sensorimotor representation of the body, Chap. II. New York: Hafner.
- Pons TP, Kaas JH (1986) Corticocortical connections of area 2 of somatosensory cortex in macaque monkeys: a correlative anatomical and electrophysiological study. *J Comp Neurol* 248:313-335.
- Pons TP, Garraghty PE, Cusick CG, Kaas JH (1985) The somatotopic organization of area 2 in macaque monkeys. *J Comp Neurol* 241:445-466.
- Pubols B, Pubols L (1971) Somatotopic organization of spider monkey somatic sensory cerebral cortex. *J Comp Neurol* 141:63-76.
- Randolph M, Semmes J (1974) Behavioral consequences of selective subtotal ablations in the postcentral gyrus of *Macaca mulatta*. *Brain Res* 70:55-70.
- Robinson CJ, Burton H (1980) Organization of somatosensory receptive fields in cortical areas 7b, retroinsula, postauditory, and granular insula of *M. fascicularis*. *J Comp Neurol* 192:69-92.
- Roland PE (1976) Astereognosis. *Arch Neurol* 33:543-550.
- Sakata H, Takaoka Y, Kawarasaki A, Shibutani H (1973) Somatosensory properties of neurons in the superior parietal cortex (area 5) of the rhesus monkey. *Brain Res* 64:85-102.
- Sakata H, Taira M, Murata A, Mine S. (1995) Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. *Cerebral Cortex* 5:429-438.
- Schwartz A (1983) Functional relationship between somatosensory cortex and specialized afferent pathways in the monkey. *Exp Neurol* 79:316-328.
- Shanks MF, Pearson RCA, Powell TPS (1985) The callosal connexions of the primary somatic sensory cortex in the monkey. *Brain Res Rev* 9:43-65.
- Shoham D, Grinvald A (2001) The cortical representation of the hand in macaque and human area S-1: high resolution optical imaging. *J Neurosci* 21:6820-6835.
- Sinclair RJ, Burton H (1991) Neuronal activity in the primary somatosensory cortex in monkeys (*Macaca mulatta*) during active touch of textured surface gratings: responses to groove width, applied force, and velocity of motion. *J Neurophysiol* 66:153-169.
- Slutsky DA, Manger PR, Krubitzer L (2000) Multiple somatosensory areas in the anterior parietal cortex of the California ground squirrel (*Spermophilus beecheyii*). *J Comp Neurol* 416:521-539.
- Snyder LH, Batista AP, Andersen RA (1997) Coding of intention in the posterior parietal cortex. *Nature* 386:167-170.
- Stepniewska I, Pruess TM, Kaas JH (1993) Architectonics, somatotopic organization, and ipsilateral cortical connections of the primary motor area (M1) of owl monkeys. *J Comp Neurol* 330:238-71.
- Sur M, Nelson RJ, Kaas JH. (1980) Representation of the body surface in somatic koniocortex in the prosimian Galago. *J Comp Neurol* 189:381-402.
- Sur M, Nelson RJ, Kaas JH (1982) Representations of the body surface in cortical areas 3b and 1 of squirrel monkeys: comparisons with other primates. *J Comp Neurol* 211:177-192.
- Taoka M, Toda T, Iwamura Y (1998) Representation of the midline trunk, bilateral arms, and shoulders in the monkey postcentral somatosensory cortex. *Exp Brain Res* 123:315-322.
- Taoka M, Toda T, Iriki A, Tanaka M, Iwamura Y (2000) Bilateral receptive field neurons in the hindlimb region of the postcentral somatosensory cortex in awake macaque monkeys. *Exp Brain Res* 134:139-146.
- Toda T, Taoka M (2001) The complexity of receptive fields of periodontal mechanoreceptive neurons in the postcentral area 2 of conscious macaque monkey brains. *Arch Oral Biol* 46:1079-1084.
- Toda T, Taoka M (2002) Integration of the upper and lower lips in the postcentral area 2 of conscious macaque monkeys (*Macaca fuscata*). *Arch Oral Biol* 47:449-456.
- Tremblay F, Ageranioti-Belanger SA, Chapman CE (1996) Cortical mechanisms underlying tactile discrimination in the monkey. I. Role of primary somatosensory cortex in passive texture discrimination. *J Neurophysiol* 76:3382-3403.
- Veenman C, Reiner A, Honig M (1992) Biotinylated dextran amine as an anterograde tracer for single- and double-label studies. *J Neurosci Methods* 41:239-254.
- Vogt BA, Pandya DN (1978) Cortico-cortical connections of somatic sensory cortex (areas 3, 1 and 2) in the Rhesus monkey. *J Comp Neurol* 177:179-192.
- Welles JF (1976) A comparative study of manual prehension in anthropoids. *Saugetierkundliche Mitteilungen* 24:26-38.
- Wise SP, Boussaoud D, Johnson PB, Caminiti R (1997) Premotor and parietal cortex: corticocortical connectivity and combinatorial computations. *Annu Rev Neurosci* 20:25-42.
- Wu CW-H, Kaas JH (2003) Somatosensory cortex of prosimian galagos: physiological recording, cytoarchitecture, and corticocortical connections of anterior parietal cortex and cortex of the lateral sulcus. *J Comp Neurol* 457:263-292.