

THE INTRAPARIETAL SULCUS OF THE MACAQUE AND CONNECTED
CORTICAL REGIONS: ANATOMICAL PARCELLATION AND
CONNECTIONS THROUGHOUT THE HEMISPHERE

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ABSTRACT OF THE DISSERTATION

The general aim of this thesis was to better characterize anatomical connections of cortical areas of the intraparietal sulcus (IPS) in the macaque monkey, which is a region implicated in visual and somatosensory integration and motor intention. The anatomical organization of the IPS and regions with which it is connected was investigated with structural and connectional methods. The structure of the IPS and most other portions of the cortical hemisphere were analyzed with myelin and Nissl stains, plus immunohistochemical staining with the SMI-32 antibody. Primarily utilizing architectonic criteria defined in previous studies (with some refinements), parcellation maps were derived including up to 90 distinct cortical areas and zones. Retrograde tracers were injected into selected areas of the IPS (LIP, VIP, and AIP), superior temporal sulcus (MT and MST) and parietal lobule (7a and 7b), and the distribution of labeled cells was charted in relation to the architectonic parcellation maps. These data, together with geographical landmarks (sulcal curvature) were all displayed on computer-generated three-dimensional reconstructions and on cortical flat maps.

The analysis of architecture in the IPS revealed two newly identified regions: the lateral occipito-parietal zone, LOP, previously considered part of V3A; plus 7t, characterized by strong SMI-32 immunoreactivity (previously considered part of area 7b or area 2). Additionally, medial and lateral subdivisions of area VIP are proposed (VIPm and VIPl), and significant modifications were introduced along portions of the superior temporal sulcus, and for somatosensory area 2.

Injections centered in visual area LIPv led to connections mainly with extrastriate visual areas, whereas injections centered in neighboring area VIP

(VIPl and VIPm) led to stronger connections with somatosensory, polysensory, and motor areas. The visual-related connections of VIPl largely overlapped the patterns seen in LIPv injections. Sensorimotor projections to VIP included several somatotopically organized areas or regions, predominantly from the estimated hand, arm, and to a lesser extent the face representations. Strong connections originated from several bimodal and polysensory areas, supporting its involvement in multiple highly distributed hierarchical networks relating to the integration of visual, somatosensory (sensorimotor), vestibular, and possibly auditory information.

TABLE OF CONTENTS

Acknowledgments.....	iii
Abstract.....	iv
Table of Contents.....	vi
List of Figures and Tables.....	viii
Abbreviations.....	ix
 CHAPTER 1: GENERAL INTRODUCTION	
A. Introduction.....	1
B. Clinical Studies.....	1
C. Behavioral Studies in Monkey.....	2
D. Organization of Parietal Cortex in Monkey.....	3
E. Background of Area VIP.....	4
F. Networks that May Involve VIP.....	8
G. Summary.....	10
H. References.....	11
 CHAPTER 2: ARCHITECTONIC PARCELLATION OF PARIETO- OCCIPITAL CORTEX AND INTERCONNECTED CORTICAL REGIONS IN THE MACAQUE MONKEY	
A. Abstract.....	18
B. Introduction.....	20
C. Materials and Methods	23
1. Animals.....	23
2. Intracardial Perfusion.....	23
3. Histological Processing.....	24
4. Computerized Reconstructions and Neuroanatomical Analyses.....	26
5. Electrophysiological Recording.....	29
D. Results.....	31
1. Architectonic Organization of the Intraparietal Sulcus.....	31
2. Variability in the IPS/POS.....	52
3. Architectonic Maps of the Cortical Hemisphere.....	63
4. Parcellation of the Cortical Hemisphere.....	82
5. Areal Heterogeneity.....	102
6. Correlations Across Different Stains.....	103
E. Discussion.....	105
1. Comparisons to Previous Architectonic Studies.....	106
2. Global Parcellations and Flat Maps.....	110
F. Literature Cited.....	112
G. Appendix A: Architectonic Parcellation of Cerebral Cortex in the Macaque Monkey.....	126
1. Visual Cortex.....	127
2. Somatosensory Cortex.....	143
3. Cingulate Cortex.....	149
4. Motor and Premotor Cortex.....	151
5. Prefrontal Cortex.....	154
6. Auditory-related Cortex.....	157

CHAPTER 3: CORTICO-CORTICAL CONNECTIONS OF VISUAL, SENSORIMOTOR, AND MULTIMODAL PROCESSING AREAS IN THE PARIETAL LOBE OF THE MACAQUE MONKEY

A.	Abstract.....	160
B.	Introduction.....	162
C.	Materials and Methods.....	165
	1. Surgical Procedures.....	165
	2. Data Analysis, Architectonics, and Unfolding.....	167
	3. Tracer Injection Analysis.....	168
D.	Results.....	171
	1. Case A.....	172
	2. Case B.....	185
	3. Case C.....	202
	4. Case D.....	207
	5. Case E.....	211
	6. Case F.....	215
	7. Summary of Cortical Connections.....	218
E.	Discussion.....	232
	1. Connectivity as a Guide to Partitioning.....	233
	2. Areal Connectivity Patterns.....	235
	3. Topography of VIP.....	240
	4. Interhemispheric Connections of the IPS and STS....	242
	5. Functional Implications/Significance.....	244
F.	Literature Cited.....	246

CHAPTER 4: GENERAL DISCUSSION

A.	Functional Roles of VIP.....	260
B.	Future Directions.....	263
C.	References.....	266

LIST OF FIGURES

CHAPTER I

Figure 1	Myelin and SMI-32 Staining of 5V, VIPm, VIPl, and LIPv.....	34
Figure 2	Illustration of Coronal, 3D, and 2D Formats.....	36
Figure 3	Flat map showing areas and zones of the IPS.....	38
Figure 4	Myelin and SMI-32 Staining of LOP, V3A, V3, PIP, and PO.....	44
Figure 5	Myelin and SMI-32 Staining of zone 7t.....	46
Figure 6	Myelin and SMI-32 Staining of AIP.....	48
Figure 7	Myelin Staining of MDP from 3 cases.....	50
Figure 8	Examples of Staining Variability of 5V, VIP, and LIPv.....	57
Figure 9	Examples of Staining Variability of LOP, V3A, and V3.....	59
Figure 10	Four flat maps of IPS Illustrating Variability.....	61
Figure 11	Coronal Sections Through Hemisphere of Case 95DR.....	67
Figure 12	Flat Map of Case 95DR with Curvature and Architecture Maps..	71
Figure 13	Comparison of parcellations in previous studies.....	73
Figure 14	Flat Map of Case 94CR with Curvature and Architecture Maps..	79
Figure 15	Flat Map of Case 93IR with Curvature and Architecture Maps..	81
Figure 16	Myelin and SMI-32 Staining of Posterior STS.....	86
Figure 17	Myelin and SMI-32 Staining of Anterior STS.....	88
Figure 18	Myelin and SMI-32 Staining of Posterior Lateral Sulcus.....	91
Figure 19	Staining and Physiological Mapping of Area 2.....	94
Figure 20	Myelin and SMI-32 Staining of Ventral Arcuate Sulcus.....	99
Figure 21	Myelin and SMI-32 Staining of Cingulate Sulcus.....	101

CHAPTER III

Figure 1	Projections to VIPl on 3D and Flat Map (Case A).....	176
Figure 2	Projections to VIPl, Coronal Sections (Case A).....	178
Figure 3	Projections to LIPv, 7b, and VIPl (Case A).....	180
Figure 4	Projections to VIPm on 3D and Flat Map (Case B).....	188
Figure 5	Projections to VIPm and AIP, Coronal Sections (Case B).....	192
Figure 6	Projections to AIP and MSTdp (Case B).....	196
Figure 7	Contralateral Projections to VIPm, AIP, and MSTdp (Case B)....	201
Figure 8	Projections to LIPv and LIPd/7a/7b (Case C).....	205
Figure 9	Projections to MT and MT/MSTdp (Case D).....	210
Figure 10	Projections to 7a, LIPv/VIP, and VIP/AIP (Case E).....	214
Figure 11	Projections to VIP/5V and Anterior LIPv (Case F).....	217
Figure 12	Summary of VIP Connections.....	229
Figure 13	Networks Involving the IPS.....	231

LIST OF TABLES

CHAPTER III

Table 1	Summary of Injections.....	170
Table 2	Connections of VIPl (Case A).....	182
Table 3	Connections of VIPm (Case B).....	189
Table 4	Summary of Connections.....	221

ABBREVIATIONS

Cortical Areas:

A1	primary auditory cortex
AIP	anterior intraparietal area
DP	dorsal prelunate area
ER	entorhinal cortex
FST	floor of superior temporal area
G	gustatory cortex
Ia	agranular insular cortex
Id	dysgranular insular cortex
Ig	granular insular cortex
IPa	area IPa from Cusick et al., (1995)
LIPd	lateral intraparietal (dorsal)
LIPv	lateral intraparietal (ventral)
M2	motor area 2 (also supplementary motor cortex)
MDP	medial dorsal parietal area
MIP	medial intraparietal area
MST	medial superior temporal area
MT	middle temporal area
PIP	posterior intraparietal area
PO	parietal-occipital area
PrCO	precentral opercular cortex
PreS	prestriate cortex
R	auditory area R
Ri	retroinsula
S2 cx	second somatosensory area (complex)
SMA	supplementary motor area
TAa	area TAa from Cusick et al., (1995)
TEad	antero-dorsal division of TE
TEav	antero-ventral division of TE
TF	temporal area F
TH	temporal area H
Tpt	temporo-parietal area
TPOc	temporal parietal occipital (caudal)
TPOi	temporal parietal occipital (intermediate)
TPOr	temporal parietal occipital (rostral)
VIP	ventral intraparietal
V1	visual area 1
V2	visual area 2
V3	visual area 3
V3A	visual area V3A
V4	visual area 4
V4t	V4 transitional area
VOT	ventral occipitotemporal area
VP	ventral posterior area (V3v)
1	somatosensory area 1
2	somatosensory area 2
3a	somatosensory area 3a
3b	somatosensory area 3b
4	primary motor cortex
5	somatosensory area 5
7b	somatosensory region 7b

7a	visual area 7a (PP, PG)
23	cingulate area 23
24	cingulate area 24
35	perirhinal area 35
36	perirhinal area 36
45	Walker area 45
46	visual area 46

Cortical Zones:

LOP	lateral occipital parietal
MSTda	medial superior temporal area (dorsal, anterior)
MSTdp	medial superior temporal area (dorsal, posterior)
MSTm	medial superior temporal area (medial)
ST	superior temporal cortex
Toc	temporal opercular caudal
VIPl	ventral intraparietal (lateral)
VIPm	ventral intraparietal (medial)
V4ta	V4 transitional area (anterior)
V4tp	V4 transitional area (posterior)
7t	subdivision of 7 near tip of IPS (also 2v)
7op	opercular area 7
5V	area 5 (ventral)
5D	area 5 (dorsal)

Cortical Sulci:

ASd	arcuate sulcus, dorsal limb
ASv	arcuate sulcus, ventral limb
CaS	calcarine sulcus
CgS	cingulate sulcus
CeS	central sulcus
IOS	inferior occipital sulcus
IPS	intraparietal sulcus
LaS	lateral (Sylvian) sulcus
LuS	lunate sulcus
OTS	occipital temporal sulcus
POS	parieto-occipital sulcus
PS	principal sulcus
STS	superior temporal sulcus

Chapter 1. General Introduction

The function of parietal cortex in primates is thought to be largely involved with maintaining a spatial reference system that is in part used for guiding movements of the eyes, limbs, and head (for review, see Hyvärinen, 1982; Andersen, 1995). Additionally, the projections of parietal cortex onto motor and premotor cortex may be involved with on-line sensory feedback of arm, face, and body movements that are made in the environment. The parietal cortex has mainly been studied with regard to the visual and somatosensory modalities, and to its relationship with motor function. Integration of auditory and vestibular-related inputs may also occur based on lesion studies both in humans and monkeys. Since the cortex of the monkey is better understood and more accessible with regard to analysis of architecture, patterns of connections, and physiological response properties, the monkey serves as an excellent model for furthering our understanding of the basic organization of parietal cortex and multimodal integration in primates.

Clinical studies

Much of our understanding of the function of parietal cortex in humans is derived from studies of lesions. Bilateral damage to parietal cortex (i.e. strokes or gunshot wounds) have resulted in variety of deficits first described by Balint (1909). The deficit of Balint's syndrome includes three main characteristics: psychic paralysis, which is characterized by a patients inability to look toward a point in the peripheral visual field; optic ataxia, which is manifested as difficulty or an inability to direct the hand toward visually presented targets; and spatial attention deficits, where no defect is

present in the vision of a patient per se, but he or she would be inclined to attend visual stimuli in the right periphery rather than straight ahead. Other symptoms of parietal lesions include difficulty in avoiding obstacles when walking, counting, drawing maps or pictures as a whole. Additionally, patients tend not to see the whole of a picture or scene, but rather viewing the world in a piecemeal fashion (Holmes, 1918).

Unilateral lesions of right parietal cortex result in neglect of the contralateral visual field and body half, such that a person may not dress, shave, or tend to the left half of their body, denying that it belongs to them (Denny-Brown and Chambers, 1958). The deficits resulting from left versus right parietal cortex have much in common, in that each hemisphere largely represents the contralateral space. However, the right hemisphere is more involved with spatial analysis and body movements, while the left is more concerned with the mechanisms of language (Critchley, 1953; Denny-Brown and Banker, 1954).

Behavioral studies in monkey

In monkeys, lesions of parietal cortex (areas 5 and 7) produce similar symptoms to those in humans, though are generally less pronounced, and have not been found to have any hemispheric asymmetry. The resulting deficits largely implicate somatosensory/motor and visual integration, but also vestibular and possibly auditory modalities. Sensorimotor-related symptoms resulting from unilateral lesions include reaching deficits characterized by slowness in movement, general clumsiness in the use of the animal's contralateral limbs and arm projection on both sides of the midline (with and without visual guidance), and modification in the shaping of the hand and

fingers upon approaching a target (Peele, 1944; Fleming and Crosby, 1955; Hartje and Ettlinger, 1973; Lamotte and Acuna, 1978).

Visual-related symptoms of parietal lesions or cooling include visuospatial disorientation (characterized by difficulty in assessing the location of a target relative to other targets), eye movement deficits that impair visual search (Latto, 1978), and visual extinction, where if two stimuli are presented, one in each hemifield, the animal will ignore the one contralateral to the lesion (Stein, 1978). Unilateral neglect has also been noted in monkeys with lesions of areas 5 and 7, wherein the animal is disinclined to use the contralateral limbs, and is less reactive to tactile and painful stimuli (Peele, 1944).

Organization of parietal cortex in monkey.

Historically, parietal cortex of the macaque monkey was comprised of areas 5 and 7 (cf. Brodmann, 1907). These regions have undergone multiple re-parcellations, and currently include nearly a dozen distinct areas, many of which are buried within the intraparietal sulcus (IPS). Criteria for delineating these areas are derived from combinations of architecture, physiology, and patterns of connections. Cortex extending along postero-lateral portions of the IPS is dominated by areas high in the visual hierarchy (classic area 7). It is part of the dorsal or "where" stream (Desimone and Ungerleider, 1989), being largely involved in spatial analysis as opposed to object recognition (the "what" stream). Antero-medial portions of the IPS are occupied by high order somatosensory cortex, especially involving the arm (classic area 5). For instance, cells in area 5 have complex receptive fields, such as multiple joint interaction, bilateral interactions of the forelimbs and

body, and a wide range of limb movements (Sakata et al., 1973). Thus, this region is thought to be a site that represents the position and form of the body and limbs, and of tactile objects in three-dimensional space.

In between the predominantly visual and somatosensory regions lies a long and nearly contiguous stretch of cortex that is known or suspected to contain cells with bimodal or polymodal response properties. This includes the fundus of the IPS, and extends both to the medial wall and to parieto-temporal cortex: Specifically areas MIP and possibly MDP (7m) (Colby and Duhamel, 1991; Cavada and Goldman-Rakic, 1989), the ventral intraparietal area (VIP) (Duhamel et al., 1997), 7b (Hyvärinen and Poranen, 1974, Leinonen and Nyman, 1979), and Tpt (Leinonen et al., 1980). Bimodal area VIP lies along the fundus of the IPS, which served as a focus in this study. Detailing the connections of VIP relative to the surrounding architectonically defined areas in parietal cortex and other portions of the cerebral hemisphere offers a chance for exploring the circuitry underlying multimodal integration.

Background of area VIP

Area VIP appears to be a physiologically distinct area, yet anatomically is not well understood, primarily for two reasons. First, it is a small area buried deep in cortex, residing along the middle third of the fundus of the intraparietal sulcus. Therefore, the standard method of visually guiding a pipet to a target site to inject neuronal tracers is not possible. Instead, one must utilize alternative methods such as physiological mapping or removing obstructing cortex. The second reason is that VIP is high in the visual and somatosensory hierarchy, 6 to 9 levels up from its sensory inputs, and thus

mainly connected with areas which themselves are not well understood (and lack sharply defined borders).

Seltzer and Pandya (1986) have described an architectonic region extending across most of the fundus of the IPS (area IPd), which appears to include area VIP of this study, in addition to cortex further anterior and posterior. Area VIP was originally defined by its connections with area MT (Maunsell and Van Essen, 1983), which revealed a projection zone located in and around the middle third of the fundus of the intraparietal sulcus. Although the architectonic borders of VIP were not examined in their study, the connectivity features were considered distinctive enough to warrant calling the projection zone a separate cortical area.

In subsequent studies, the issue has been raised that the MT projection zone of the IPS may include more than one architectonically and physiologically distinct area. For instance, Ungerleider and Desimone (1986) observed connections between MT and a densely myelinated area they termed VIP*, located on the lateral wall of the IPS, in addition to the region along the floor of the fundus. This densely myelinated area has subsequently been identified as area LIPv by Blatt et al., (1990), who also reported connections with this area and MT (also see Colby and Duhamel, 1991). Thus, the MT projection zone in the IPS is likely to include at least two distinct cortical areas.

Connectivity of estimated VIP. Previous connectivity studies have demonstrated that the fundal region of the IPS is connected with both visual and somatosensory areas (Pandya and Kuypers, 1969; Pandya and Seltzer, 1982; Seltzer and Pandya, 1980). Though area VIP was not explicitly mapped in earlier studies, the estimated location of VIP was found to connect with visual-

related areas V2 and V4 (Seltzer and Pandya, 1980), V3 and VP (Felleman et al., 1997), PO (Seltzer and Pandya, 1980; Colby et al., 1988), MDP (7m) and 7a (Pandya and Seltzer, 1982; Seltzer and Pandya, 1986), plus saccade-related areas LIPd and LIPv (Blatt et al., 1990). Connections with visual motion-related areas in the posterior half of the STS include MT (as described above), FST and various subdivisions of MST (Ungerleider and Desimone, 1986; Boussaoud et al., 1990), and polysensory area TPOc (TPO-4, Seltzer and Pandya, 1991).

From sensorimotor-related cortex, moderate connections with the estimated location of VIP include cortex near the tip of the IPS (Pandya and Seltzer, 1982), area 5 and 7b (Seltzer and Pandya, 1986), and premotor cortex (Tanné et al., 1995). Lighter connections may include the hand and arm representations of somatosensory areas 1 and 2 (Burton and Fabri, 1995; Pearson and Powell, 1985; Seltzer and Pandya, 1980), and of primary motor cortex (area 4, Leichnetz, 1986).

Physiology of VIP. The visual response properties of VIP neurons were characterized by Colby et al., (1993). They describe VIP as containing a high incidence of selectivity for the direction of a moving stimulus. Also, VIP cells are selective for speed of stimulus motion, and are responsive to whole-field motion. These response properties distinguish VIP from the surrounding cortex (areas 5, LIPv, AIP, and PIP), and are similar to the response properties of areas MT, MST and other regions of the superior temporal sulcus (STS). Additionally, some VIP neurons respond best to a stimulus moving toward the animal, particularly when the anticipated point of contact of the stimulus is on the animal's face. A minority of VIP cells are selective for the distance at which a stimulus is presented, often preferring "ultra-near" stimuli, within 5 centimeters of the animal's face. This response property is consistent with the

behavior resulting from a unilateral lesion of VIP, which includes a deficit selective for near stimuli (Duhamel et al., 1997), such as drinking from a water bottle with only the ipsilateral side of the mouth (Dr. Colby, personal communication).

VIP cells differ markedly from cells in the STS and from neighboring area LIP (and PIP) in that VIP has somatosensory-related response properties (Colby and Duhamel, 1991). Roughly three quarters of VIP neurons can be independently driven by stimulation of somatosensory receptive fields found primarily on the face and head, ranging in size from 1 to 8 cm² (Duhamel et al., 1997). Cells respond to passive superficial stimulation of the skin surface and hair, and many show a preference for the direction of the tactile stimulation. Small tactile receptive fields are typically centered near the lips and nose (the somatosensory "fovea"), while larger receptive fields are located on the top or side of the head, or neck. Some cells are responsive to joint rotation of the hand and upper limb, though are minor in number relative to cells with a face or head representation.

More striking is that many VIP neurons have visual and somatosensory receptive fields that tend to correlate with one another in size and location, as described by the above authors. For instance, the top of the face corresponds with upper visual field representations, and the lower face and sometimes arm or hand tactile receptive fields correspond with the lower visual field. Together, the above properties led the above authors to propose that VIP has a role in subserving eye/hand and mouth coordination, such as with feeding behaviors (Colby et al., 1993).

Networks that may involve VIP.

Other regions of the macaque brain show visual plus somatosensory (bimodal) response properties similar to those of VIP, including 7b (Hyvärinen and Poranen, 1974; Leinonen and Nyman, 1979), premotor cortex (peri-arcuate area 6, Rizzolatti et al., 1981a,b), the putamen (Graziano and Gross, 1994), and possibly temporal cortex along the STS (TPO, Mistlin and Perrett, 1990). Areas 7b, premotor cortex, and the putamen are known to contain somatotopic maps (including at least arm/hand representations in addition to the face), and together with VIP may represent the animal's extrapersonal space in a somatotopic fashion (Graziano and Gross, 1994).

Studies of premotor cortex have suggested separate networks for visually guided reaching versus grasping, which is supported by connections with parietal cortex (Tanné et al., 1995). Specifically, area VIP, together with visual areas LIP, PO, 7a, and MDP, were found to be connected with dorsal premotor cortex, which is involved with visually guided reaching network. In contrast, neighboring somatosensory-related areas AIP and portions of area 5 are connected with ventral premotor cortex, which is involved with grasping-related behaviors (Tanné et al., 1996). The region of cortex in the vicinity of VIP, AIP, and LIP contains cells responsive to hand movements (Taira et al., 1990), though the connections of this region are not well understood.

A vestibular network? Currently, there does not appear to be a discrete vestibular sensation, but vestibular cortical afferents are integrated with other sensory modalities concerning, for instance, the spatial relations of our head and body with the environment (cf. Akbarian et al., 1994). Parietal cortex (both in human and monkey) may integrate vestibular information to

the extent that lesions result in defects in recognition of posture (spatial orientation with respect to the body) and also in tactile localization (orientation in the extrapersonal space) (Head, 1920; Schwarz and Fredrickson, 1974). Graf et al., (1996) found that roughly a third of VIP neurons show vestibular sensitivity, and that the preferred directions for vestibular and optokinetic activation are in the same direction (non-complementary). They concluded that VIP may be signaling overcompensation of eye or head movement responses, and/or detecting constant spatial coordinates. This finding raises the possibility that VIP may be connected with a network of vestibular-related cortical areas, such as those known to connect directly with vestibular nuclei shown by Akbarian et al., (1994). Such a pattern is likely to emerge in the analysis of VIP connectivity patterns.

An auditory network? Immediately dorsal to area VIP lies area LIP, which is predominantly visuo-motor in function though appears to be involved with integrating information from auditory stimuli. For instance, LIP neurons are responsive to auditory cues, pertaining to "remembering" the location of an auditory target to which the animal must make a saccade (Andersen, 1995; Linden et al., 1996). Since LIP and VIP appear to have a similar roles in representing the three-dimensional space around the animal (possibly encoding intention for eye and somatic movements, respectively), it seems likely that VIP too might integrate auditory information. However, auditory-related connections with LIP or VIP remain to be established.

S u m m a r y

Clinical, behavioral and electrophysiological data indicate that parietal cortex is involved with maintaining a spatial reference system with regard to visual, somatosensory and vestibular-related modalities, motor function, and possibly the auditory modality. Several distinct parietal areas are thought to play different roles in the process of sensory integration, one of which is area VIP. The cortico-cortical connections of VIP are presently not well understood. This thesis addresses the architecture and connections of the intraparietal sulcus so as to serve as a guide for more precise behavioral and electrophysiological investigation.

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CHAPTER 2: Architectonic Parcellation of Parieto-occipital Cortex and Interconnected Cortical Regions in the Macaque Monkey

ABSTRACT

The intraparietal sulcus (IPS) of the macaque monkey contains numerous areas that are associated with different aspects of cortical function, including motor control as well as visual, somatosensory, and perhaps auditory processing. This study analyzes the architectonic organization of areas within the IPS and regions with which it is connected. Cortical areas plus gyral and sulcal geography were visualized on computationally generated flat maps, which facilitated the analysis of consistent as well as variable aspects of the sizes and relative positions of areas across cases.

Using myelin and Nissl stains, plus immunohistochemical staining with the SMI-32 antibody, 17 architectonic subdivisions were identified that are largely or entirely contained in the intraparietal and parieto-occipital sulci. This includes four newly identified regions: a heavily myelinated lateral occipito-parietal zone, termed LOP (previously considered part of V3A); a small, strongly SMI-32 immunoreactive zone termed 7t (previously considered part of area 7b); plus VIPm and VIPl, which are the medial and lateral subdivisions of VIP, respectively (previously regarded as a single area). Additionally, we identified areas V3, V3A, PIP, PO, MIP, LIPd, LIPv, 5V (PEa), 5D, MDP, 7a (PG), 7b (PF), and AIP.

Our analysis of architecture in other regions of the hemisphere confirmed many previously identified subdivisions, identified some new ones, and provided revised or supplemental criteria for identifying many others. Within

the superior temporal sulcus, this includes a newly identified subdivision MSTdp, (dorsal and posterior to areas MT and MST), and a dorsal inferotemporal region, ITd, along the ventral bank. The borders of somatosensory area 2 near the IPS were revised based on combined architectonics and physiological recordings. Altogether, we were able to chart the full or partial extent of up to 90 areas and architectonic zones over a region covering most of the cortical hemisphere.

INTRODUCTION

Cerebral cortex of the macaque monkey is a complex mosaic of many distinct areas that can be distinguished on the basis of architecture, patterns of connectivity, topography, and physiological properties. The strongest cases for defining an area exist when two or more criteria support the same partitioning, and other criteria do not overtly conflict. However, the literature is replete with competing partitioning schemes, and includes many "areas" that were identified using only a single type of criterion. For example, the borders of areas MDP and CITd are based on patterns of connections alone (Colby et al., 1988; Van Essen et al., 1990), while the borders of area 31 are largely based on architecture alone (Vogt et al., 1987).

Each of the above approaches to defining an area can be ambiguous, especially architectonics, because of intrinsic heterogeneity known to exist within the boundaries of well defined areas, such as the thick and thin stripes of V2 (cf. Livingstone and Hubel, 1984; DeYoe et al., 1990). This is especially problematic in regions physically further from primary areas (at more advanced stages of processing), which tend to show more ambiguous architectonic features. Higher areas also tend to be smaller than primary and secondary sensory areas, yet the modularity reported within an area is coarser in at least some cases (Carmichael and Price, 1994). This makes it difficult to distinguish unambiguously between different areas versus subdivisions of a single area. Another problem arises from variability in the robustness and consistency of architectonic boundaries from animal to animal. Despite these caveats, architectonic analysis remains an invaluable guide for assessing the overall layout of cortical areas and landmarks, especially in the face of individual variability. Regardless of the semantics of how regions are labeled,

consistently identifiable architectonic landmarks or zones are likely to have functional significance, and hence be useful for furthering our understanding of cortical organization.

In the parietal lobe, multiple partitioning schemes have been described, based largely on cytoarchitectonic and myeloarchitectonic criteria (von Bonin and Bailey, 1947; Jones et al., 1978; Pandya and Seltzer, 1982; Seltzer and Pandya, 1986; Colby et al., 1988; Blatt et al., 1990; Preuss and Goldman-Rakic, 1991b). Within and near the intraparietal sulcus (IPS), nearly a dozen areas have been identified or proposed. Together, these areas comprise a major site where visual, somatosensory, and possibly other modalities (sensory and motor) integrate. The lateral bank of the IPS receives inputs predominantly from the dorsal stream of the visual system (Ungerleider and Mishkin, 1982), while the medial bank receives predominantly somatosensory inputs, including cells responsive to complex hand and arm movements (Sakata et al., 1973; Mountcastle et al., 1975; Iwamura et al., 1994). Some of the architectonically defined areas of the IPS are further distinguished by differential patterns of connections and/or by physiologically defined transitions (Colby and Duhamel, 1991; Colby et al., 1993; Blatt et al., 1990; Seltzer and Pandya, 1986). However, the number and areal extent of many areas and putative subdivisions of the IPS are still unclear or poorly characterized both in architecture and patterns of connectivity.

In the present study, we re-examined the architecture of cortex in and near the IPS, and of regions throughout the hemisphere which are connected with intraparietal cortex (Chapter 3). In addition to cyto- and myeloarchitectonic parcellation, our analysis was aided by immunohistochemical techniques, including the SMI-32 immunoreactivity and CAT-301 immunoreactivity. The SMI-32 antibody has been shown to

differentiate numerous areas of visual cortex (cf. Hof and Morrison, 1995; Cusick et al., 1995) and frontal cortex (Carmichael and Price, 1994). Similarly, the CAT-301 antibody differentially stains regions of visual and somatosensory cortex (McGuire et al., 1989; DeYoe et al., 1990). With the combined analysis of these four techniques, several newly defined regions and some significant modifications from previous studies are presented, involving regions throughout all lobes of the hemisphere.

To reduce confusion in how distinct architectonic regions are labeled, we distinguish "areas" from "zones." The term "area" is applied to cortical regions that are largely consistent with distinct areas identified in previous studies (especially when supported by independent criteria). We use the term "zone" to denote a region that can consistently be identified in our architectonic analysis, but where our data are insufficient to determine whether it is a distinct cortical area, part of a larger architectonically heterogeneous area, or may itself contain multiple subdivisions.

As a tool for analyzing and representing the architectonically derived areal boundaries of cortex, we use computationally derived two-dimensional maps (flat maps) of nearly the entire hemisphere (Drury et al., 1996a). This application facilitates analysis of the total extent of areal boundaries relative to three dimensional sulcal patterns.

Some of these results have been presented as abstracts (Lewis and Van Essen, 1994, 1996).

MATERIALS AND METHODS

Animals

Results were obtained from 10 juvenile-adult Macaque fascicularis monkeys (6 females and 4 males) weighing between 2.0 and 3.8 kg. Prior to perfusion, retrograde tracers had been injected into two or three sites in or near parietal cortex in each case (one hemisphere only), as part of a companion study of the connections of intraparietal areas (Chapter 3). Also, in 3 cases, somatosensory cortex in and near the postcentral gyrus was mapped electrophysiologically to identify the digit and face representations. All procedures were performed according to protocols approved by the Animal Study Committee at Washington University or the California Institute of Technology.

Intracardial perfusion

Prior to perfusion, animals were sedated with ketamine (i.m., 10 mg/kg), and xylazine (i.m., 0.1 ml/kg). Heparin sulfate (i.v., 25,000 units) was injected, and after 5 to 10 minutes, an overdose of sodium pentobarbital was injected (i.p., 30 mg/kg and i.v., 30 mg/kg). Once deep anesthesia was attained, intracardial perfusion was initiated with a solution of 0.1M phosphate buffer, pH 7.4, with 10,000 Units/L Heparin sulfate and 40 mg/L Lidocaine (30 - 50 ml/min for 20 minutes). There followed perfusion with 4% paraformaldehyde in 0.1M phosphate buffer at pH 7.4-7.5 (15 min), buffered 4% paraformaldehyde with added increments of 10% sucrose (8 - 10 min), 20% sucrose (4 - 5 min), and 30% sucrose (optional, 2 - 5 min), and finally, 200 ml of 30% sucrose in 0.1M phosphate buffer. Brains were removed and stored until sinking at 4°C in a series of ascending sucrose solutions (10%, 20%, and 30%)

in 0.1 M phosphate buffer (total 3-5 days). The hemispheres were blocked and photographed during the 20% or 30% sucrose solution phase of sucrose equilibration.

Histological processing

Prior to sectioning, fiducial alignment marks used in subsequent 3D computer reconstructions were generated by impaling each block of cortex with electrodes or pins coated with India ink perpendicular to the plane of sectioning. Sections were cut at 60 μ m thickness on a freezing microtome, and stored refrigerated in 0.1M phosphate buffer. Blocks were cut in the coronal plane (10 hemispheres), or orthogonal to the IPS (3 hemispheres) or parasagittally plane (1 hemisphere). One-in-six series of sections were used for Nissl (Thionin) staining, Myelin staining (Gallyas, 1979), SMI-32 immunoreacted staining, and CAT-301 immunoreacted staining. In some cases, acetylcholinesterase staining (Bear et al., 1985) was performed on sections expected to contain primary auditory cortex. Low-power micrographs of histologically stained sections were obtained from a Zeiss microscope (Axioplan) and from a macrophotography system by Nikon.

SMI-32 immunoreaction. Immediately after sectioning, free-floating sections were washed at room temperature twice for 10 to 30 minutes in 0.1M Phosphate buffer. The diluent for SMI-32 antibody staining was 0.1 M phosphate buffer, 0.3% Triton X-100, 0.5 mg/ml BSA fraction V, 2% (v/v) Goat or Horse Serum. The usual working dilution of the primary antibody, SMI-32, was 1:8,000 (Sternberger Monoclonals, Inc.). Sections were then incubated with the primary antibody ranging from 1 to 4 days (typically 2 days), gently

shaken at 4°C. Sections were thoroughly washed (3X, 10 min each) in buffer and then incubated with biotinylated secondary antibody (1:100) for 1 to 2 hours, and gently shaken at room temperature. Following thorough rinsing in buffer, sections were incubated with avidin-biotin-peroxidase complex reagent (ABC elite kit: Vector Labs, Berlingame, CA) for roughly 1 hour, and again thoroughly rinsed. Sections were stained by one of two chromagens for 5 to 30 minutes. The most sensitive chromagen was, coincidentally, VIP (Vector Inc., VIP kit), which stained cells and dendrites a deep maroon. Alternatively, Vectastain (Vector Inc.) was also very sensitive, and stained cell bodies black and dendrites a dark gray. The SMI-32 monoclonal antibody, which binds to a non-phosphorylated epitope on medium and heavy chains of the neurofilament protein (Lee et al., 1988), mainly labeled cell bodies and proximal portions of basal and apical dendrites (Campbell and Morrison, 1989; Hof and Morrison, 1995).

In general, the SMI-32 immunoreactivity in our tissue appeared to be less sensitive for the smaller pyramidal cells throughout the cortical ribbon compared to other studies (Lee et al., 1988; Campbell and Morrison, 1989; Carmichael and Price, 1994; Hof and Morrison, 1995; Cusick et al., 1995). However, the differential staining patterns described herein were reproducible across multiple cases.

CAT-301 immunoreaction. The diluent for CAT-301 antibody staining was 0.1M Phosphate buffer, 3% Triton X-100, 2.5% (v/v) Horse serum. The working antibody dilution was 1:3 in 0.1M phosphate buffer of a stock solution kindly provided by Dr. Susan Hockfield. Immediately after sectioning, free-floating sections were washed in 0.1M Phosphate buffer (2X, 10 min at room temperature), then incubated in the primary antibody for 2 days, at 4°C and

gently shaken. Sections were thoroughly washed in buffer (3X, 10 min), and then incubated for 1 to 2 hours with 1:25 dilution of peroxidase-conjugated secondary antibody (Sigma Co. or Cappel). Sections were thoroughly rinsed in buffer and then incubated for 5 to 30 minutes with 0.02 - 0.05% 3,3'-diaminobenzidine tetrahydrochloride (DAB), 0.1% nickel ammonium sulfate, 0.03% hydrogen peroxide. The patterns of CAT-301 immunoreactive label were remarkably similar to those of SMI-32 antibody staining, both in overall distribution as well as relative intensities of label throughout the hemisphere (cf. McGuire et al., 1989; DeYoe et al., 1990). However, architectonic transitions in the CAT-301 processed sections were generally not as sharply defined as with SMI-32 processed sections. Thus, they supplemented and further verified architectonic transitions rather than defined them *per se*.

Computerized reconstructions and neuroanatomical analyses

Reconstructions of the cortical surface were based on tracings of cortical layer 4 (or the boundary between layers 3 and 5) in a one-in-six series of sections used for scoring retrograde tracer in the companion chapter. Using the computerized neuroanatomy software MDPlot (version 3.0, Minnesota DataMetrics), the pial and layer 4 surface contours, and fiducial alignment marks were plotted. The borders of architectonic areas, zones, and transition regions identifiable on individual histological sections were transferred to a printout of the nearest corresponding section plotted for the layer 4 contour. The extent of transition regions ranged widely, from as little as 0.2 mm to as much as 6 mm along the cortical ribbon, depending on the sectioning angle, variations in staining quality, and the inherent robustness of the particular architectonic border. In sections stained for myelinated fibers, areas varied

in the degree of radial or tangentially oriented fiber bundles versus matted appearances, and in the presence of inner (mainly layer 5) and outer (mainly layer 3) bands of fiber plexi ("bands of Baillarger"). SMI-32 immunoreactive (SMI-32-ir) cell label differentially stained many cortical areas, based on different cell sizes, laminar distribution, and overall density of labeled cells, as reported elsewhere (Lee et al., 1988; Campbell and Morrison, 1989; Carmichael and Price, 1994; Hof and Morrison, 1995; Cusick et al., 1995).

Architectonic transitions from all staining methods were taken into consideration when producing final areal boundary estimates, though preference was given to the stain(s) that best define a given area according to previous studies, unless indicated otherwise. In cortical regions with conflicting architectonic criteria, we adopted the definitions that appeared the most robust in our tissue across the 14 hemispheres used in this study. The collective set of architectonic boundary estimates for each hemisphere or cortical block were translated to a rudimentary flat map on paper, which served as a means for organizing all areal boundaries.

The resulting set of areal boundary estimates were entered as points along the layer 4 contour of the nearest corresponding plotted sections in MDPlot. Data sections were then transferred from the personal computer to UNIX workstations (Silicon Graphics R4400 Indigo 2, Mountain View, CA). Using the software package CARET (Computerized Anatomical Reconstruction and Editing Tool kit, <http://v1.wustl.edu>), neighboring sections were aligned by global translation and rotation, with reference to the fiducial alignment marks and layer 4 contours. During the initial reconstruction phase, not all portions of a section could be precisely aligned to its neighboring sections using simple translations and rotations, due to local tissue distortions from the original slide mounted tissue sections. Thus, a smoothing procedure was used

to reduce the presence of small scale "ripples" in the reconstruction and ensuing flat map. Wire-frame surface reconstructions of layer 4 were generated using a public-domain software program (Nuages) that allows the three-dimensional reconstruction of complex shapes from the contours contained in a series of sections (Boissonnat, 1988; also see Drury et al., 1996a).

Three-dimensional reconstructions were converted into topographically correct and minimally distorted flat maps using the FLATTEN software (Drury et al., 1996a). One or two cuts were introduced extending out from the corpus callosum to facilitate the flattening process, similar to previous cortical flat maps produced in this lab (Van Essen and Maunsell, 1980; Drury et al., 1996a). Minimizing distortions (multiresolution morphing) was an iterative process, and a flat map was considered sufficiently undistorted when two criteria were met. The first was that subsequent morphing iterations no longer produced significant changes, the second involved inspection of the resulting distortion maps for each case to verify that no excessively distorted regions were present. The mean distortion average of tiles ranged from 4 to 13%, comparable to values from other computer generated flat maps in our lab (ibid.). These overall distortion values were assessed by comparing the area of each tile that made up the layer 4 surface in the three-dimensional reconstruction (roughly 90,000 tiles for large cortical blocks) with the area of the corresponding tile in the two-dimensional map. Because the flat maps necessarily contain some distortions, linear distances on the flat maps are denoted as "map-cm." They correspond to actual 3D distances only where there is no linear distortion on the map.

The mean curvature of each map was calculated and used to reveal cortical geography. Briefly, the mean curvature was determined by averaging the maximum curvature value associated with each node (such as the rounded

portion of a cylinder) with a curvature value for that same node in the direction orthogonal to the maximum (i.e. along the height of the cylinder). A gray-level representation of curvature was generated by interpolating between adjacent nodes (Drury et al., 1996a).

Areal boundary points (described above) were assigned 3D coordinates and an identity. Each point was projected to the nearest tile in the 3D surface reconstruction of layer 4. By preserving this geometrical relationship, architectonic boundary points could then be positioned on the flat maps relative to the nearest tile. Architectonic boundary outlines were entered manually on the flat maps in CARET with reference to the architectonic boundary marks. The collection of areal boundary marks, however, rarely defined a smooth outline, and thus a smoothed contour running close to the innermost set of points was drawn (see Fig. 2). Outlines were used to represent the cores of architectonically defined areas or zones that have been described in previous studies or could be consistently identified across multiple cases. Transition regions and cortex of uncertain identification were excluded from these core outlines. In maps that include most of the cortical hemisphere, several thousand architectonic border transitions contributed to the outlines of core areas and zones in the final cortical map. Descriptions of each architectonic area and zone distinguished in this study are presented in Appendix A, and at our WWW site (<http://v1.wustl.edu>).

Electrophysiological recording

In three experiments, post-central somatosensory cortex was electrophysiologically mapped to identify the digit and face representations and physiologically identifiable areal boundaries in the vicinity. Animals

were initially anesthetized with ketamine (10 mg/kg i.m.), and administered glycopyrolate (11 mg/kg i.v.) and dexamethasone (0.27 mg/kg i.v.). Surgery was carried out under isofluorane anesthesia (2-5% with air), and animals were artificially respired and monitored for expired CO₂, heart rate, and core temperature. A unilateral craniotomy was made over the post-central gyrus, and the exposed cortex was covered with siloxane. For electrophysiological recording, anesthesia was switched to Sufentanil (4 - 8 µg/kg/hr) in an intravenous solution including Sufentanil Citrate, 0.02 mg/ml Dexamethasone, 0.9% NaCl, and 2.5 - 5% glucose.

Multiunit responses were recorded with Tungsten electrodes (A-M Systems, Inc.). Tactile receptive fields were characterized and assigned to somatosensory areas using criteria similar to those described by Pons et al., (1985) and Burton and Fabri, (1995). Area 1 responses were characterized by cutaneous responses on the digits by using a fine paint brush stimulus. Area 2 was responsive to deeper stimulation (gently prodding with the back end of the paint brush), and was less responsive or not responsive to cutaneous stimulation. Cortex posterior to area 2 (probably area 5), near and along the anterior bank of the IPS, was characterized by cells that were best driven with fast movements or joint movement, and were not driven by cutaneous or prodding stimulation. Electrodes were coated near the tip with India ink to mark their tracks. Electrolytic microlesions were placed at a few recorded regions to further assist in track reconstruction.

RESULTS

In each hemisphere, we identified up to 90 areas and zones throughout most of the cortical hemisphere, including several previously unreported zones and subdivisions. Our analysis starts with the intraparietal/parieto-occipital region, which was studied the most intensively, and also used to illustrate the multiple formats in which data are represented and analyzed. Five other geographic regions are then discussed, including temporal cortex, the lateral sulcus, somatosensory cortex, premotor and prefrontal cortex, and cingulate cortex. Architectonic features of each area and zone are further detailed in Appendix A.

Architectonic organization of the intraparietal sulcus

Our criteria for architectonic parcellation of cortex in and near the intraparietal sulcus (IPS) were based largely on the descriptions by Blatt et al., (1990) for areas of the lateral bank of the IPS, including LIPv, LIPd, and 7a, by Colby et al., (1988) for posterior areas MIP, PO, PIP, V3A, and MDP, by Van Essen et al., (1986) for V3, by Preuss and Goldman-Rakic, (1991b) for AIP, and Jones et al., (1978) for area 5.

Figure 1 shows myelin and SMI-32 processed coronal sections at two antero-posterior levels of the IPS of case 95DR. In both pairs of sections there is a strong correlation between the density of myelination in a given region (particularly in layers 3-5) and the density of SMI-32 immunoreactive (SMI-32-ir) cell label in layers 3 and 5. For example, in coronal sections midway along the IPS (Figs. 1A and 1B), there were two heavily myelinated regions, one corresponding to LIPv (Blatt et al., 1990) on the lateral bank, and another

that we identify as zone VIPm (the medial portion of area VIP), on the medial bank. Both of these subdivisions showed strong SMI-32 immunoreactivity in this section (Fig. 1B), though this tended to be more robust and consistent in LIPv than in VIPm. Cortex along the fundus, zone VIPl, appeared lighter both in myelin stains and SMI-32-ir cell density. Area LIPd was also more lightly myelinated (dorsal to LIPv on the lateral bank), typically showing well separated bands of Baillarger. The ventral-most portion of area 5, termed zone 5V (dorsal to VIPm on the medial bank) showed myelination and SMI-32-ir cell label that was lighter than VIPm, though the relative density of each stain was variable along the antero-posterior axis (typically denser overall in area 5 in sections further anterior, as addressed below).

In addition to the more salient staining features evident in Figures 1A and 1B, several additional characteristics of each area helped in identifying boundaries. For example, zone 5V had pronounced inner and outer bands of Baillarger that were well separated from each other along the antero-posterior extent of the IPS, whereas VIPm was characterized by a single thick and matted band of myelination in layers 3 through 5. This laminar distinction was more reliable as a cortical transition marker than the overall density alone. Another important distinction evident in Figure 1A, is that the gray matter of LIPv tends to be thicker than in neighboring areas LIPd and VIPl, giving it a bulged appearance. This feature, which is most prominent in posterior portions, is unlikely to be an artifact of cortical folding *per se* (cf. Blatt et al., 1990), and thus also served as a useful marker.

Figure 1. Coronal sections through middle and posterior portions of the IPS of case 1 (95DR), stained for myelinated fibers (A, C) and stained with the SMI-32 antibody (B, D). Bars along white matter indicate transition regions between cortical areas and zones. Dorsal is up and lateral to the right. Panel scale bar is 1 mm. Left inset shows a drawing of the brain, indicating the approximate location of the pairs of sections. Middle and right insets are drawings of the coronal sections nearest the sections in panels C and A, respectively. The box indicates the location of the photographs. Inset scales are 1 cm.

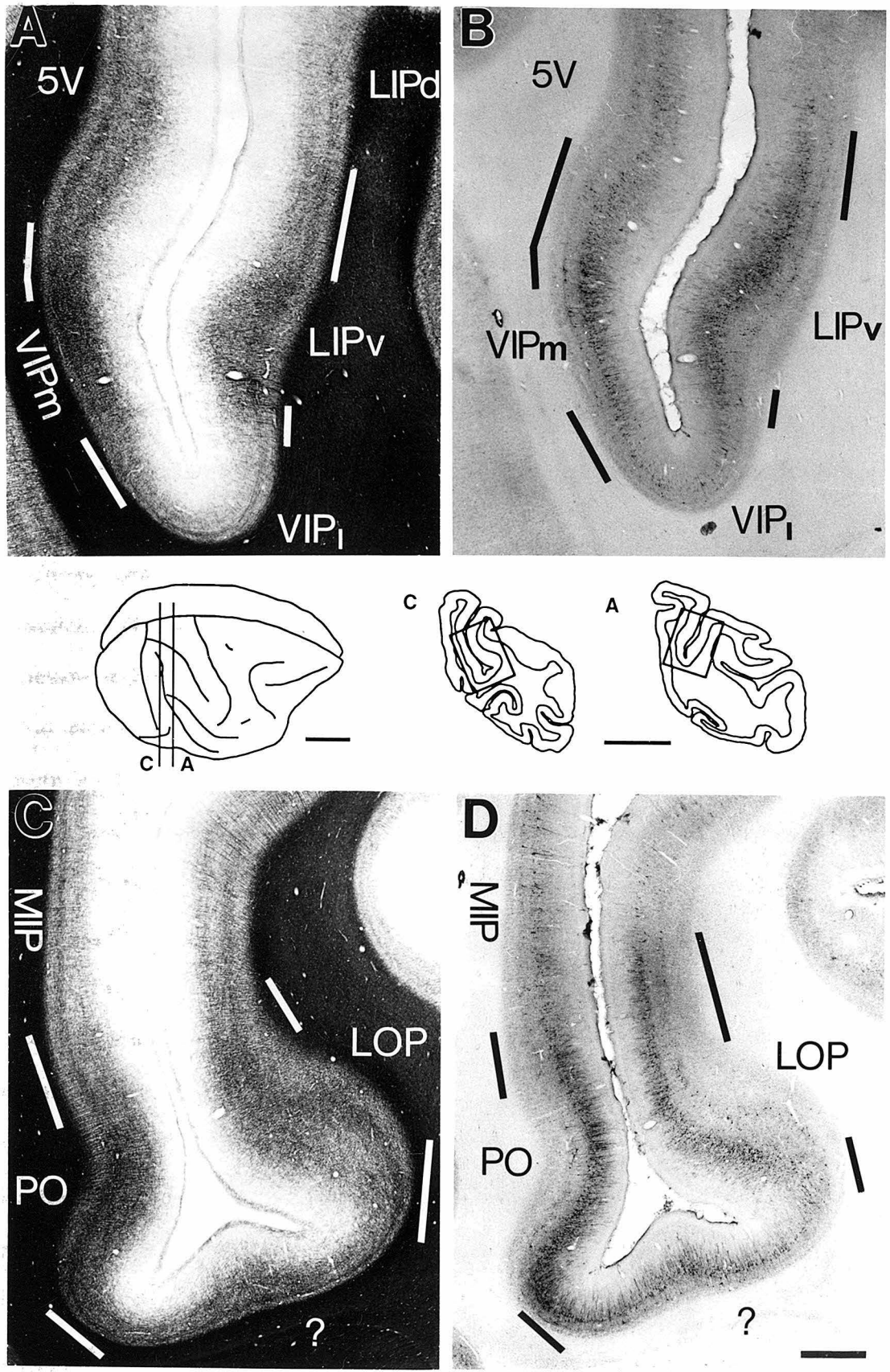


Figure 2. Illustration of the transition from coronal sections with architectonic data to the flat map representation. (A, B) Drawings of coronal sections showing several architectonic boundaries. The pial surface and boundary between gray and white matter are indicated by solid lines. Dashed lines represent layer 4 or the boundary between layers 3 and 5, and is the contour used for generating reconstructions of cortical blocks. Shaded regions indicate transitional architecture. The final border estimates indicated were derived from the combined analysis of four histological stains, and thus may differ from the transitions indicated in any one section from Figure 1. Scale bar is 1 cm. (C) Lateral view of right hemisphere of case 95DR. (D) A slightly smoothed three-dimensional computer reconstruction of 95 coronal sections spaced 360 micrometers apart, with the sections in panels A and B indicated. (E) A highly smoothed version of the same cortical block, revealing much of the buried cortex. (F) Unfolded map of cortex produced according to method of Drury et al., (1996a). The curvature map reveals the sulcal pattern evident in panels D and E. To reduce surface distortions, one cut (dashed lines) was introduced along the medial wall, posterior to the corpus callosum. In all flat maps, anterior is to the right, and dorsal and medial are roughly up. (G) Illustration of transitional cortex ("error bars") surrounding cortical area LIPv. (H) Distortion map illustrating regions of expansion (lighter shades) and contraction (darker) (refer to methods). The residual distortions tend to lie along the perimeter of the map (for example the white region in lower right edge of map). Minor local compressions are common along the fundi and expansions along the sulcal ridges. The scale cross for the flat maps is 1 map-cm, and is accurate for portions of the map that are undistorted.

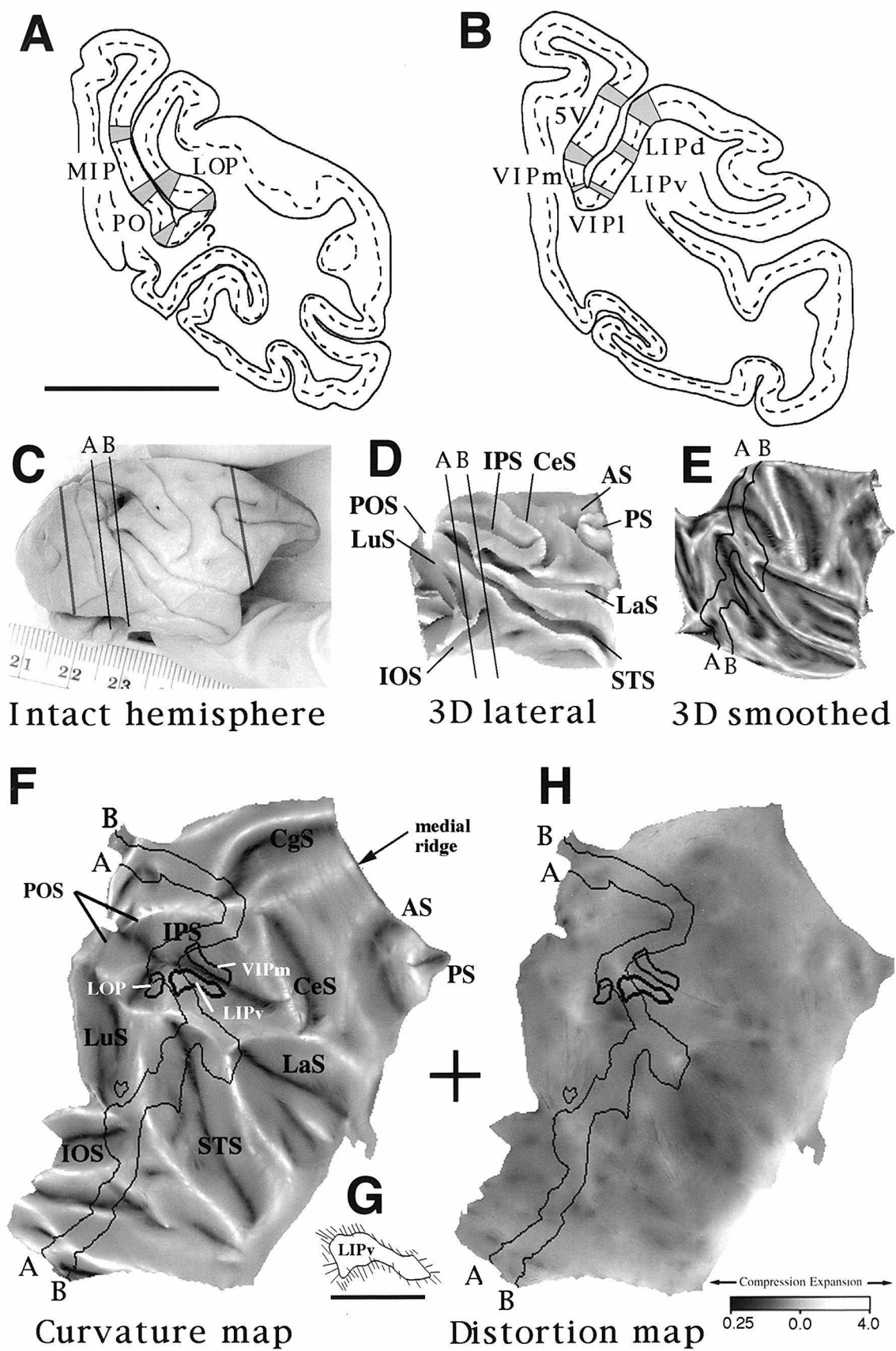
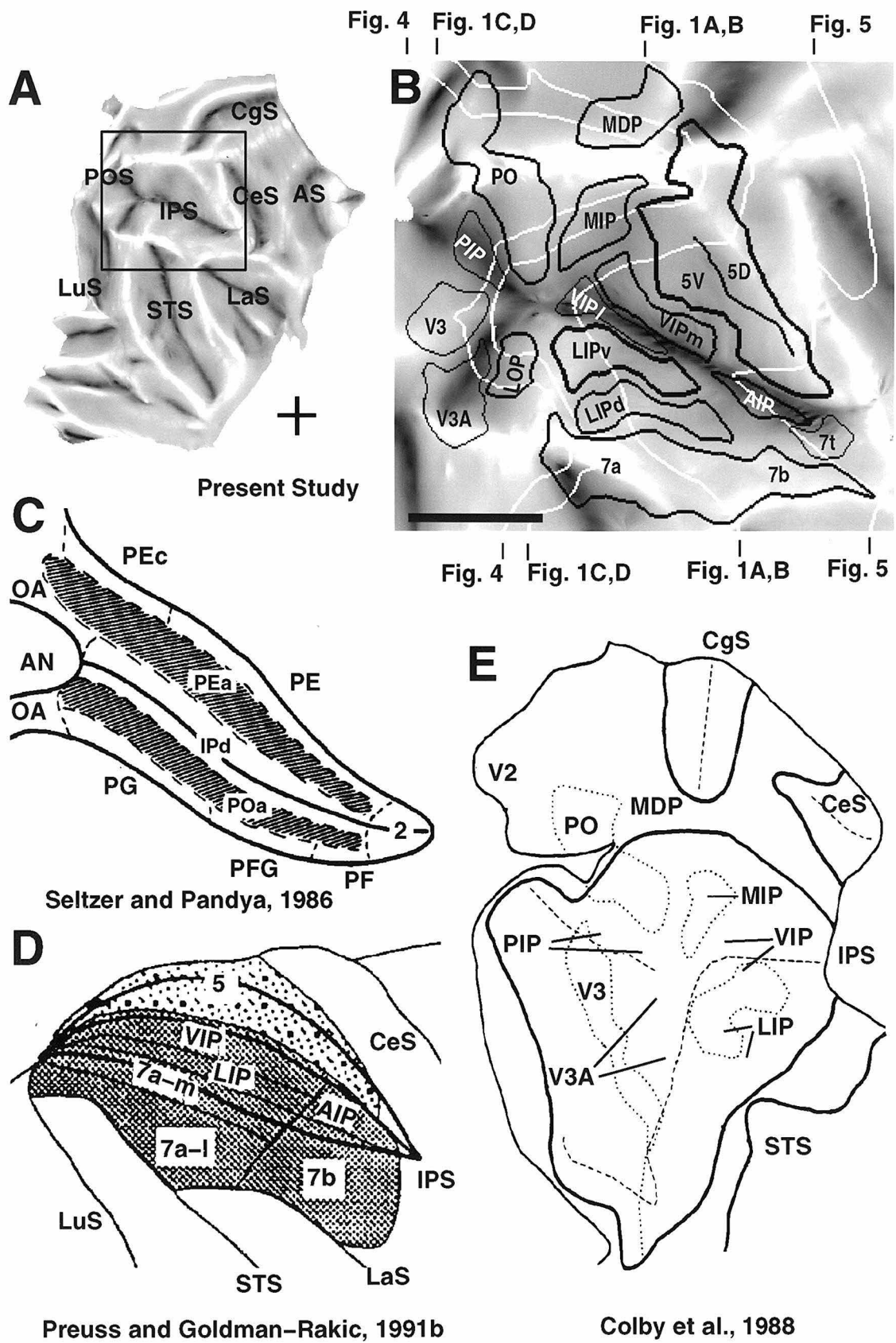


Figure 3. Present and previous parcellations of parieto-occipital cortex (all oriented as right hemispheres to facilitate comparisons. (A) flat map of case 95DR with curvature from Figure 2F. (B) Expanded view of the parieto-occipital region, with seventeen architectonically identified areas. The total extent of V3 proper and V3A proper may fall outside the expanded region illustrated, based on geography. White contours indicate location of sections illustrated in this report. Scale bar and cross are 1 map-cm. Other conventions as in Figure 2. (C) Seltzer and Pandya (1986) defined IPd along the fundus, which overlaps AIP, VIP, and possibly portions of PIP in the present study. PEa overlaps much of 5V, and POa overlaps LIPv and LIPd. (D) Preuss and Goldman-Rakic (1991b) introduced area AIP and refinements on area 7. (E) Colby et al., (1988) introduced areas PO and MIP (dotted outlines) which were adopted in this study. The dotted outline of VIP and LIP probably correspond with LIPv of the present study. Dashed lines represent fundi, and broad lines represent the sulcal ridges.



Figures 1C and 1D illustrate a different set of architectonic subdivisions in more posterior portions of the IPS. On the medial bank, area PO was characterized by relatively heavy myelination with a strong radial component (Colby et al., 1988) and strong SMI-32-ir cell label with a relatively broad layer 3 (Hof and Morrison, 1995). On the lateral bank, a newly designated zone LOP (lateral occipital parietal) was also characterized by its relatively dense myelination and by a correspondingly dense pattern of SMI-32-ir label, especially in layer 3. Cortex along the fundus (Fig. 1C) was more lightly myelinated than either PO or LOP, but was scored as transitional because it was not identifiable as part of adjoining areas V3A or PIP. Dorsal to PO on the medial bank, is a lightly myelinated area identified as MIP, also distinguished by a thin, prominent inner band of Baillarger (Colby et al., 1988). Cortex dorsal to LOP on the lateral bank was designated as transitional in this section, probably belonging to LIP or DP.

In Figure 1, the pattern of myelination and SMI-32-ir label in LOP appears similar to that seen in LIPv. However, the two were separated by a narrow region of sparser SMI-32-ir cell label on intervening sections, and LOP extended further posterior than the location of the posterior border for LIPv (Blatt et al., 1990). Additionally, LIPv generally had a stronger radial component as compared with the more matted appearance in LOP (also see Figs. 8 and 9). Differences in connections also support this subdivision (cf. Chapter 3).

Flat map representation. Starting with the sections shown in Figure 1, Figure 2 illustrates the progression from individual coronal sections to a three-dimensional reconstruction, and from there to a cortical flat map of case 95DR. Panels A and B show section drawings of the two levels illustrated in Figure 1 (3.6 mm separation), with the dashed line indicating the contour of

layer 4. In both sections, several architectonically distinct zones and areas (labels) and transition regions (gray wedges) are indicated along the IPS.

Figure 2C shows a photo of the right hemisphere, and Figure 2D shows a corresponding layer 4 computer reconstruction of most of that hemisphere, excluding a portion of the frontal lobe and the tip of the temporal pole that were in a different tissue block, and all of area V1 (deleted from the reconstruction to reduce distortions upon flattening). The location of the coronal sections shown in panels A and B are indicated. Figure 2E shows the same reconstruction after extensively smoothing the surface, thereby revealing much of the cortex buried within sulci. The original surface geometry is represented using a gray-level map of mean curvature, in which darker shades represent "inward folds", where the crease occurs along the fundus of a sulcus, and lighter shades represent "outward folds", where the crease occurs along the sulcal ridges (Drury et al., 1996a).

Figure 2F illustrates the two-dimensional map (flat map) for the cortical block in panels D and E. Cortical geography is represented by the mean curvature, allowing easy matching of corresponding sulci in all three display formats. To facilitate comparisons across all flat maps (left or right hemisphere), cingulate cortex is positioned along the top (corpus callosum at top center), frontal cortex is to the right, ventral temporal cortex is along the bottom, occipital cortex to the left (V2 being the left most area), and parietal cortex lies in the upper left quadrant. The contours from the sections in panels A and B are indicated, and the areal boundaries of architectonically defined VIPm, LIPv, and LOP are illustrated to facilitate visualization of the relationship between coronal sections and the flat map representation. Figure 2G shows the extent of the transition region surrounding the core outline of area LIPv. The innermost set of points are used to define a relatively smooth

contour (though some post-flattening adjustments in border delineation have been made). Figure 2H shows a map of areal distortion, in which darker shades represent compressions, and lighter shades represent expansions.

In Figure 3, panels A and B show the location of seventeen architectonic areas and zones in this study that were identifiable in the IPS, POS, and neighboring gyral regions of parieto-occipital cortex in case 95DR. Panels C through E represent three alternative parcellations of this same region proposed previously by Seltzer and Pandya (1986) (Fig. 3C), Preuss and Goldman-Rakic (1991b) (Fig. 3D), and Colby et al., (1988) (Fig. 3E). Overall, there is agreement in the location of several architectonic transitions along the IPS (despite differences in nomenclature).

In the present study, the core of a given area or zone is enclosed by a black outline, indicating a region of cortex that was confidently identified by architectonic criteria. Heavy lines outline areas whose boundaries overall were particularly robust in this hemisphere, whereas finer lines denote areas or zones characterized by more subtle architectonic transitions. The gap separating the outlines of any two regions ranged from 0.5 mm, where transitions are sharp and consistent between sections, to 5 mm in regions where transitions were subtle and compounded by oblique sectioning or irregular folding. Most areas were delineated by completely enclosing core regions, though some contained internal heterogeneity, such as zone 5D. The boundary between areas 7a and 7b was difficult to distinguish in most hemispheres (especially with coronal sections), and was often left without an explicit border marking.

Of the seventeen areas and zones identified in case 95DR, eight are in regions known from physiological studies to be largely or entirely visual (V3, V3A, PIP, LOP, PO) or visuomotor (7a, LIPd, LIPv) (cf. Felleman and Van Essen,

1991); three are predominantly somatosensory-related (5V, 5D, AIP: cf. Preuss and Goldman-Rakic, (1991b); and six are known or suspected to be multimodal, including visual and somatosensory response properties (VIPm, VIPl, and MIP: Colby and Duhamel (1991); MDP (7m) Cavada and Goldman-Rakic, (1989); 7b, Leinonen et al., (1979); and possibly 7t, Leinonen and Nyman, (1979)). Most of these core regions had an elongated shape with the long axis paralleling the folding of the sulci. For example, zones VIPm and VIPl, and areas LIPv and LIPd all had an elongated axis that lay roughly parallel to the fundus of the IPS. Figure 3B shows the location of the two contours representing the sections illustrated in Figure 1, and two contours that contain the architectonic boundaries illustrated in Figures 4 and 5 below.

Figure 4 shows two coronal sections from the parietal-occipital confluence including PO, PIP, V3, V3A, and LOP, again from case 95DR. Areas PO, V3, and zone LOP were characterized by relatively dense myelination and SMI-32 immunoreactivity. Area V3 appeared matted and densely myelinated (Van Essen et al., 1986), which correlated well with the broad and dense band of SMI-32-ir label in layer 3. Area V3A was characterized by relatively light myelination with thin bands, and a strong tangential fiber component (Colby et al., 1988). This feature correlated with light SMI-32-ir cell label, and often a distinctive, thin band of SMI-32-ir label in layer 3 (also see Fig. 9). Along the medial fundus, area PIP was characterized by lighter myelination (Colby et al., 1988) and lighter SMI-32-ir cell label than areas V3 and PO.

Figure 5 shows a coronal section through the anterior portion of the IPS illustrating a newly identified zone designated as 7t, which occupies the ventro-lateral shoulder of the IPS near its tip (hence 7t). This region may correspond to a vestibular-sensitive region termed 2v (Schwarz and Fredrickson, 1971, 1974; Akbarian et al., 1994), though due to its

Figure 4. Coronal sections from parieto-occipital-lunate confluence of case 95DR stained for myelinated fibers (**A**) and SMI-32-ir cells (**B**). The panels illustrate PO, PIP, V3, V3A, and LOP. Inset scales are 1 cm, panel scale is 1 mm. Other conventions as in Figure 1.

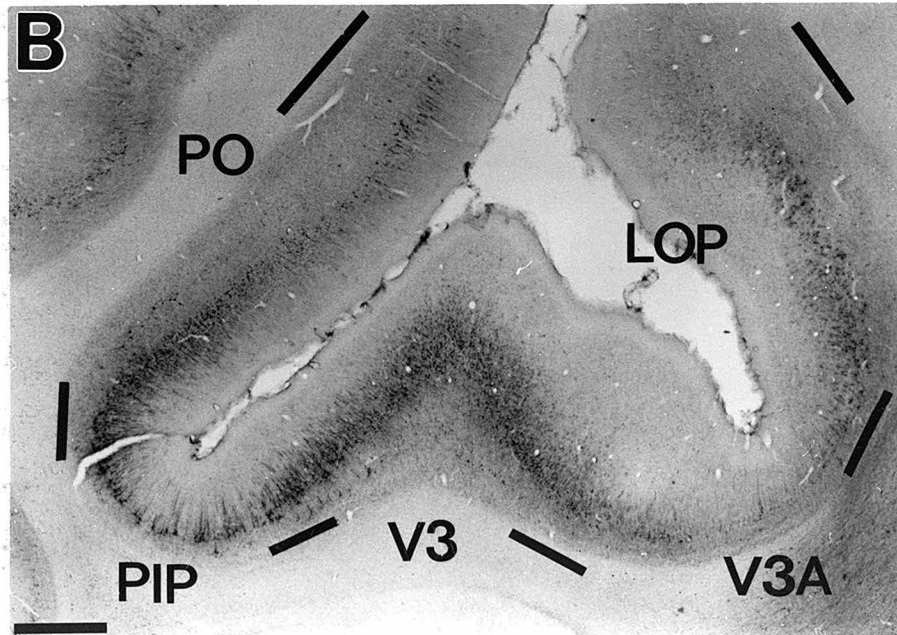
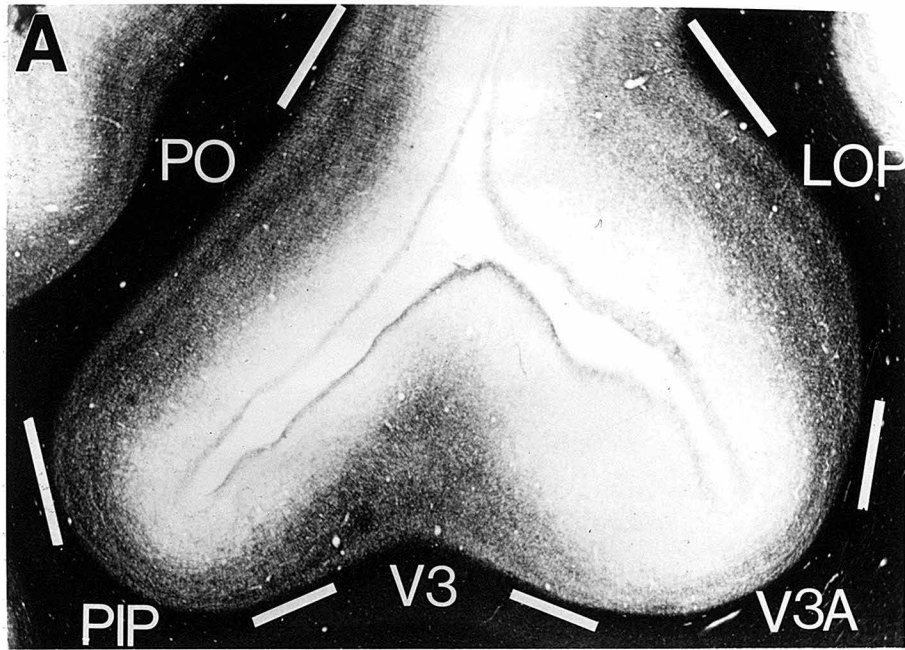
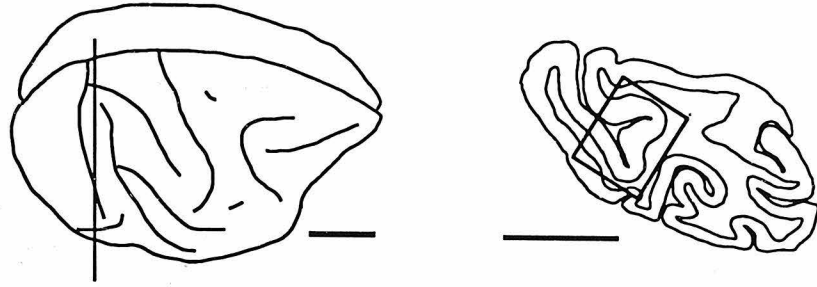


Figure 5. Coronal sections through the anterior portion of the IPS (case 95DR) stained for myelinated fibers (**A**) and stained with the SMI-32 antibody (**B**). The panels illustrate zone 7t, in addition to areas 7b, 5, and 2. Inset scale is 1 cm, panel scales are 1 mm. Other conventions as in Figure 1.

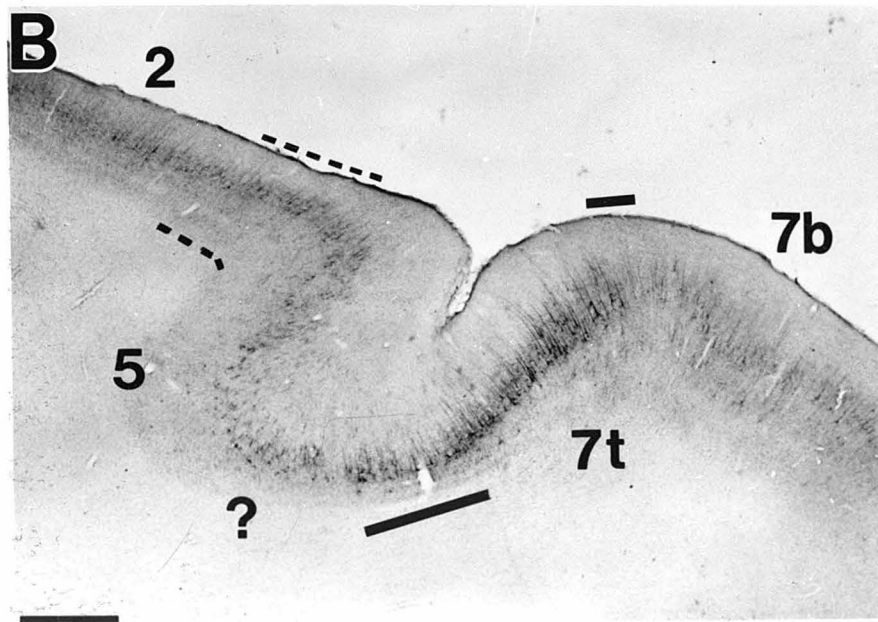
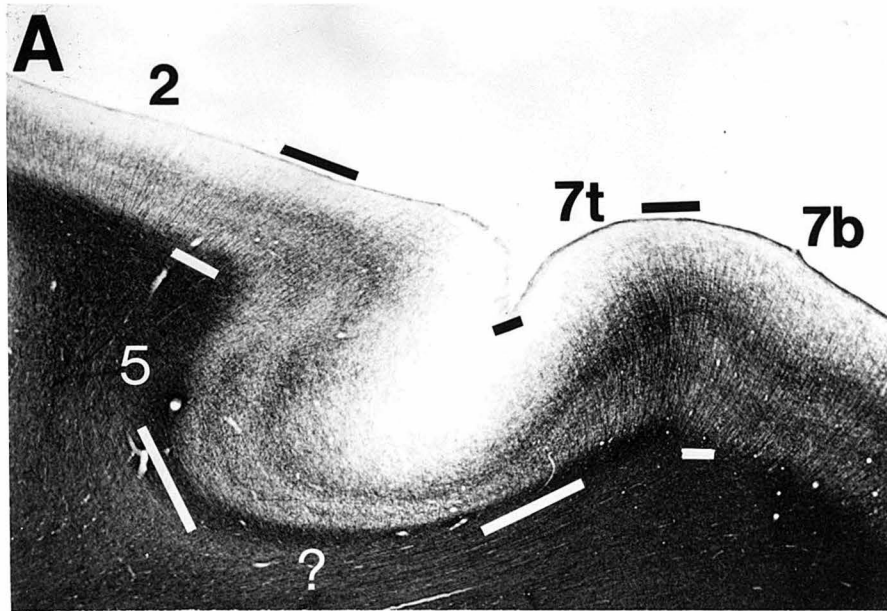
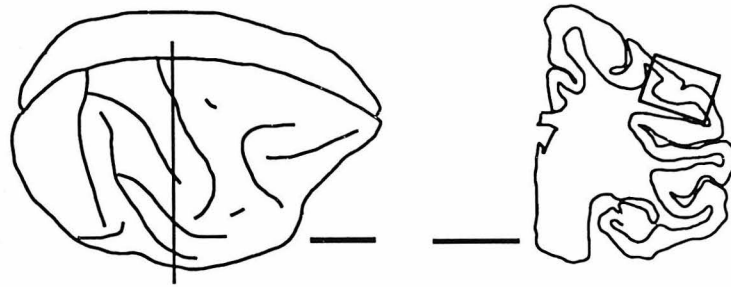


Figure 6. Coronal sections through anterior portions of the IPS (case 93IR) stained for myelinated fibers (**A**) and SMI-32-ir cells (**B**), illustrating area AIP relative to areas 5 (5V) and 7b. Panel scale is 1 mm, and inset scales are 1 cm.

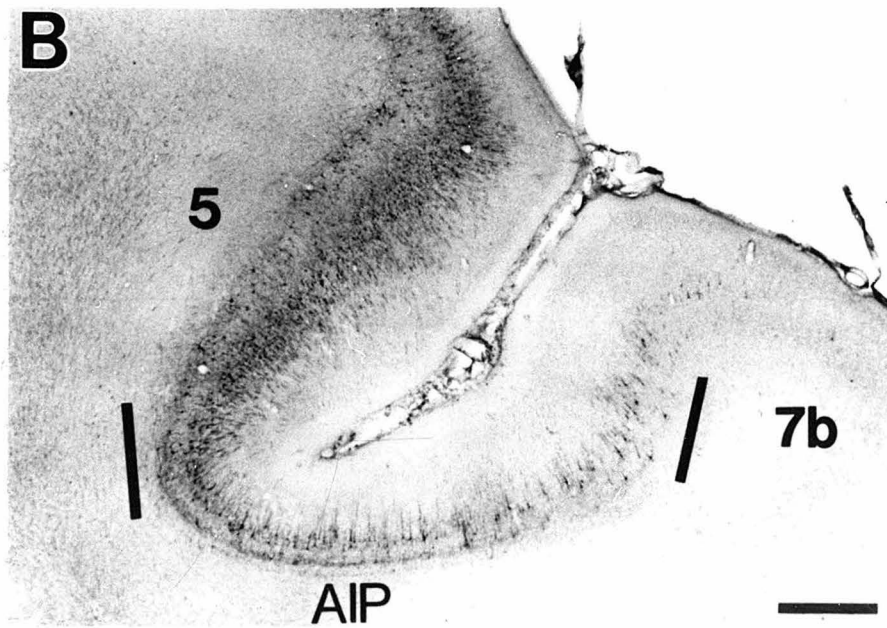
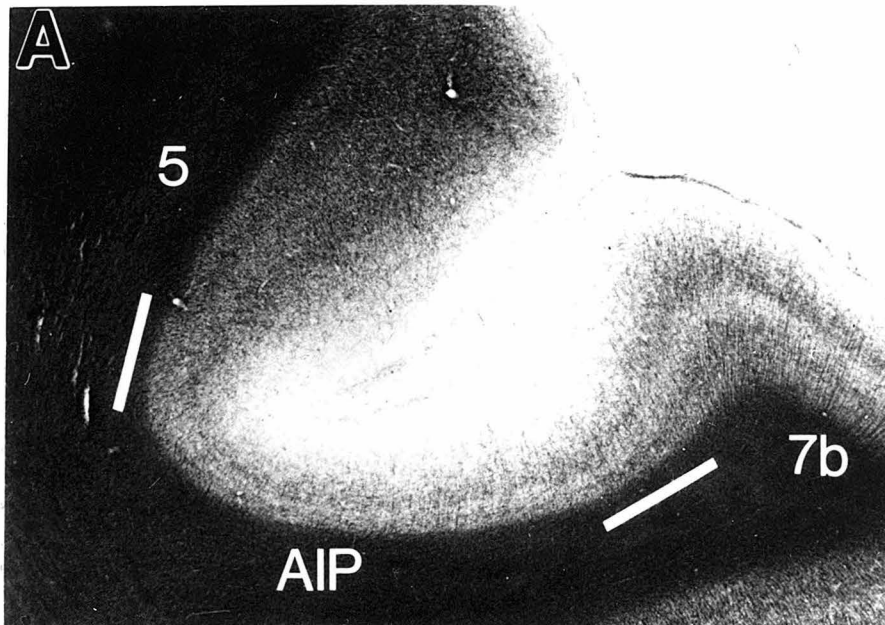
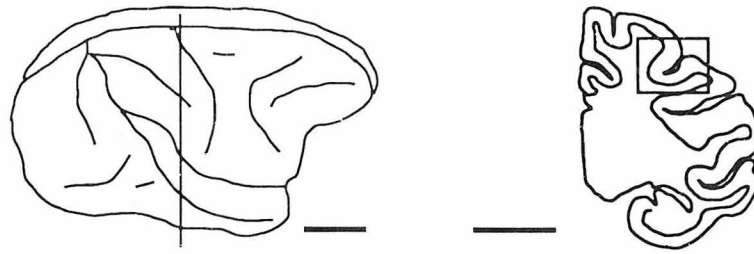
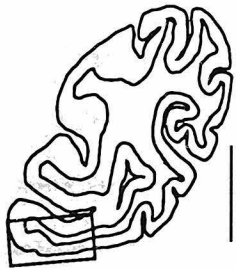
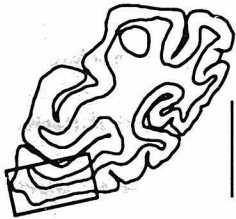
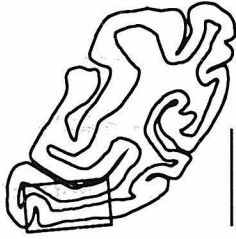
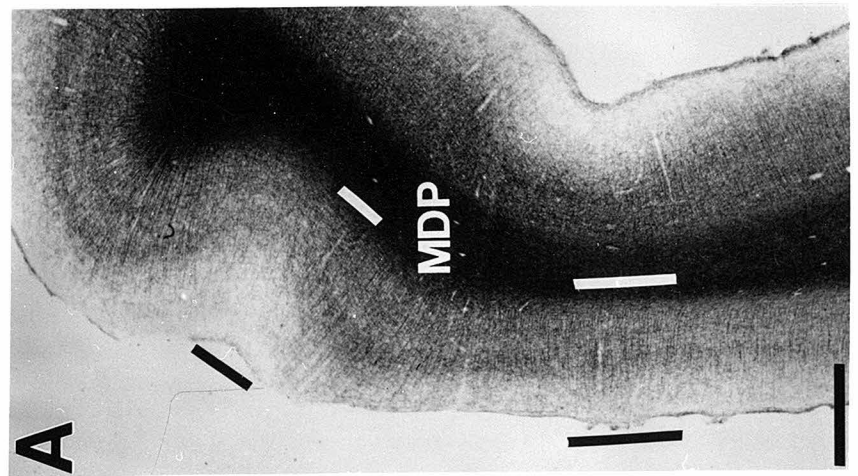
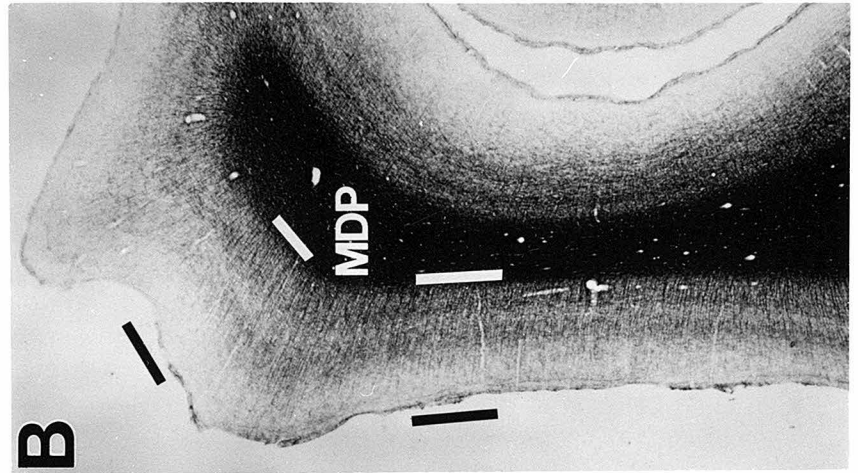
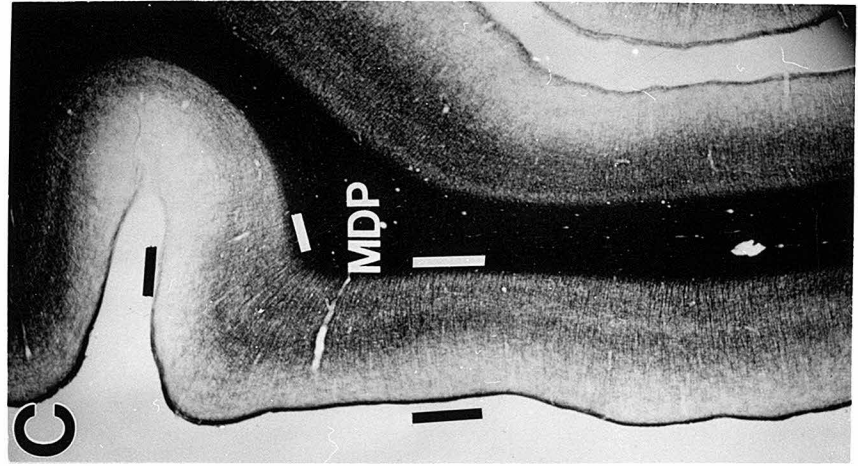


Figure 7. Coronal sections from three different cases illustrating area MDP. (A) case 94IR, (B) case 94CR, (C) case 95DR. Differences in staining details are attributable to perfusion, protocol, and animal variability. All three examples were from portions of MDP that projected to area VIP or 7a/7b (Chapter 3). Panel scale is 1 mm, inset scales are 1 cm.



myeloarchitectonic similarity and proximity to 7b, the area 7 root was retained. Zone 7t was best characterized by an increased density of SMI-32-ir cells in layer 3 that was conspicuous relative to surrounding cortex. The apical dendrites were often prominent, extending to upper portions of layer 3. This pattern correlated with a prominent and heavily myelinated outer band of Baillarger.

Figure 6 illustrates the architectonic boundaries of area AIP from case 93IR, bordering areas 5 and 7b. AIP was delineated primarily by its relatively light myelination, in which the two bands of Baillarger are poorly separated (Preuss and Goldman-Rakic, 1991b). AIP was also characterized by relatively small and sparsely distributed SMI-32-ir cells in layers 3 and 5, which were more densely populated than in area 7b, but much lighter than in area 5 (5V). Note that the dense myelination of 7b corresponds with a very light distribution of SMI-32-ir cell label, which was a characteristic observed in all cases, marking one of the few areas (also 7a) in dorsal portions of the hemisphere that show a reverse correlation in myelin and SMI-32-ir cell density.

Figure 7 illustrates three examples (different cases) of the myeloarchitecture along the medial wall in the region we identified as area MDP based primarily on its location in relation to the description by Colby et al., (1988). For each case, area MDP had relatively prominent inner and outer bands of Baillarger, slightly denser myelination than in surrounding regions, and a strong radial component. The radial bundles were present in cortex ventral to the sulcal ridge of the cingulate sulcus, and is thus not likely to represent a simple folding artifact. In SMI-32 stained sections, MDP was variable, often containing slightly denser label than surrounding areas, including sparsely distributed small to medium-large sized pyramidal cells in

layer 3 and to a lesser extent layer 5 (not shown). MDP overlapped dorsal portions of area 7m (cf. Stanton et al., 1977; Preuss and Goldman-Rakic, 1991b), and may represent a dorsal subdivision of 7m. The borders of MDP were supported by connectivity data (Chapter 3).

Variability in the IPS/POS

The various areas and zones of the IPS could be recognized consistently across hemispheres, even though the absolute staining pattern was variable from case to case, and some areas and zones were better defined than others. Figures 8 and 9 illustrate additional examples of staining patterns of the IPS in locations similar to those of Figures 1 and 4, respectively. Figure 8 illustrates areas LIPd, LIPv, and zones VIPl, VIPm, and 5V. The sulcal folds of the IPS showed variation in overall shape, both along the antero-posterior axis of any given hemisphere, and across animals. Area LIPv showed consistently denser myelination than surrounding cortex, but was variable in its radial component, the separation and distinctness of the two bands of Baillarger, and in its width along the dorso-ventral axis. Area LIPd consistently showed two moderately to lightly myelinated bands of Baillarger, and was always more lightly myelinated than LIPv. Along the fundus of the IPS, the medial portion was often characterized by denser myelination than the lateral portion (panel B), thus distinguishing VIPm and VIPl. However, in some sections and some cases, the transition was gradual, especially in myelination. The dashed line in panel A indicates the expected location of the VIPm/VIPl transition based on neighboring sections. Zone 5V consistently showed two well separated bands of Baillarger, which best distinguished it from VIPm. However, the overall density of myelination in 5V varied along the antero-posterior extent

of the sulcus, with anterior portions of area 5 generally being more densely myelinated than VIPm (i.e., see Fig. 6).

As with myelin stained sections, SMI-32-ir cell label was most robust in LIPv, having a broad and densely populated band of cells in layer 3 (Fig. 8C). In Figure 8D, the prominent cortical bulge of LIPv was not present, though the dense band of SMI-32-ir cell label in layer 3 and to a lesser extent layer 5, was still present, and was correlated with dense myelination in a neighboring section (not shown). Area VIP showed a gradient of SMI-32-ir cell label density that was slightly greater in VIPm than VIPl (panels C and D), which correlated with myelination. As in myelin stains, the VIPm/VIPl transition was not evident in some cases. However, the opposite trend in relative density was not observed in any of the cases examined. Zone 5V contained two well separated bands of SMI-32-ir cell label, and typically showed a more developed band of labeled cells in layer 5. The SMI-32-ir cell density in VIPm was usually comparable in overall density to 5V.

Figure 9 illustrates additional examples of zone LOP, areas V3A, and portions of area V3 (panels A and C illustrate closely space myelin and SMI-32 processed sections from case 94IR). As mentioned earlier, the portion of V3A that lies along the lunate-parietal confluence was identified by its relatively light myelination. In some sections, a separate outer band was evident (panel A), though a single band spanning layers 3 through 6 was more common (panel B). V3A also showed a thin, distinct band of SMI-32-ir cell label in layer 3, which was sparser than surrounding cortex in all cases examined. Area V3A contrasts in architecture with the zone LOP, in that LOP had consistently denser SMI-32-ir label, a broader and more prominent band of label in layer 3 and scattered cell label in layer 5 (Figs. 1 and 9). The LOP/V3A transition was often more robust in SMI-32 sections than myelin, though LOP was often

readily identified by its dense myelination, especially in the outer band of Baillarger. Area V3 showed a dense and matted appearance in myelination (Fig. 9B) (Van Essen et al., 1986), though in some cases showed a slight banded appearance and light radial component throughout its extent (Fig. 9A). The SMI-32-ir cell label of V3 was consistently denser than cortex further medial, lateral and anterior, and in some cases was more robust than the corresponding myelin borders (Fig. 9D).

To evaluate both the consistency and the variability in overall size, shape, and relative positions of various areas and zones in and around the IPS, Figure 10 shows the pattern of areal boundaries in four hemispheres. With regard to geography, each flat map of the IPS showed a consistent wedge-like shape, and was surrounded by readily identified sulci, including the cingulate, central, lateral, superior temporal, lunate, and parieto-occipital. However, the sulci differ significantly in overall size and shape on the maps. While some of this may reflect differences in linear distortions in flattening of the maps, there are some genuine differences that were affirmed by measurements made on 3D reconstructions. For instance, the combined depth of both banks of the IPS in panel A is roughly 20 mm, which is about 25% greater than the combined depth of the IPS in panel C (16 mm). The lengths of the IPS in these two cases, however, were about the same (measured from the juncture with the fundus of the POS to the tip of the IPS), resulting in a sharper wedge-shaped IPS in panel C (case 94CR). Additionally, in panel D, the post-central dimple was more pronounced than in the other cases illustrated. Other variations in the degree of curvature were also evident along minor folds within some of the major sulci. Despite individual differences in sulcal morphology, the architectonic areas around the IPS maintain relatively consistent positions in relation to geographic landmarks.

The relative positions of the seventeen core outlines identified in the IPS/POS region were similar in all four hemispheres. Additionally, the approximate shapes and sizes of the outlined core areas were similar across hemispheres (within a factor of 2). The outline thickness of a core area reflects the robustness of its identification in that particular hemisphere. For example, area LIPd has a thin outline in panel B (left hemisphere of case 95D), where it was more difficult to distinguish from LIPv and 7a, and a medium thickness outline in panel A (right hemisphere of case 95D), where the distinction was more robust.

Note that the size of each core region represents a lower bound estimate for the actual extent of cortex that is likely to be occupied by a given "area", as the outlines did not include the transitional regions (also see Fig. 2). The degree of underestimation will be larger for areas surrounded by wider transition regions.

Of the seventeen areas illustrated in each panel of Figure 10, areas LIPv, MIP, AIP, and zones VIPm and VIPl were the most reliably localized with respect to sulcal folds. Area LIPv was the most readily identified landmark in the parieto-occipital region, occupying the posterior half of the IPS. The dorsal and ventral borders of LIPv could be identified with relatively sharp transitions in coronal sections, though the posterior border with LOP was more variable (2 to 4 mm gap). The anterior border of LIPv also showed variability, characterized by a gradual decrease in myelination density. The anterior-most extent of LIPv correlated with the anterior limit of the cortical bulge in Figure 10A and 10B, but extended anterior to the bulge (line segment) in Figures 10C and 10D. The subdivisions VIPl and VIPm were readily distinguished in some cases (i.e., panel A). In others, where the border was not distinguishable in many sections, the open line contours within VIP indicate the approximate

Figure 8. Coronal sections through the IPS stained for myelinated fibers (**A**, case 94CR; **B**, case 94IR) and SMI-32-immunoreactive cells (**C**, case 93IR posterior; **D**, case 93IR anterior), illustrating individual variation of zones 5V, VIPm, VIPl, and areas LIPv and LIPd. In panel B, cortex of 7a is evident, characterized by a radial component stronger than in LIPd. Dorsal is to the upper left, and lateral to the upper right. The differences in SMI-32-ir staining features illustrated in Figures 1 and 8 was in part be due the degree of fixation (i.e., case 93IR had least amount of exposure to fixative and greatest amount of SMI-32-ir cell label). However, other factors may have included slight variations in protocol specifics and genuine individual variability. Scale is 1 mm.

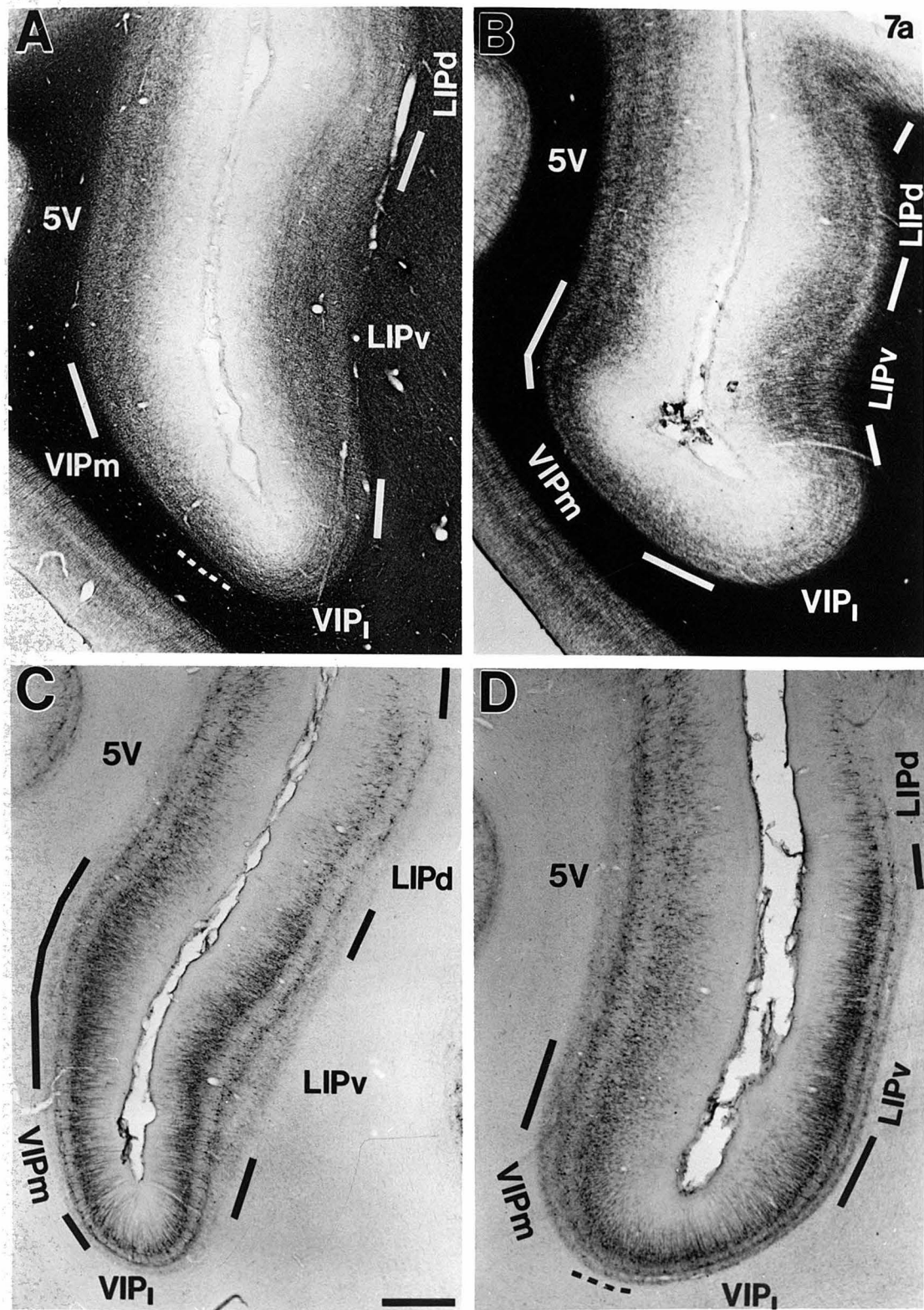


Figure 9. Coronal sections through the IPS stained for myelinated fibers (**A**, case 94IR, posterior; **B**, case 94IR, anterior) and SMI-32-immunoreactive cells (**C**, case 94IR; **D**, case 93IR), illustrating individual variation in areas LOP and V3A. Area V3 is evident in panels B and D, but were less certain in panels A and C. Area PO is also evident in panel D. Scale bar is 1 mm. Dorsal is up, and lateral to the right.

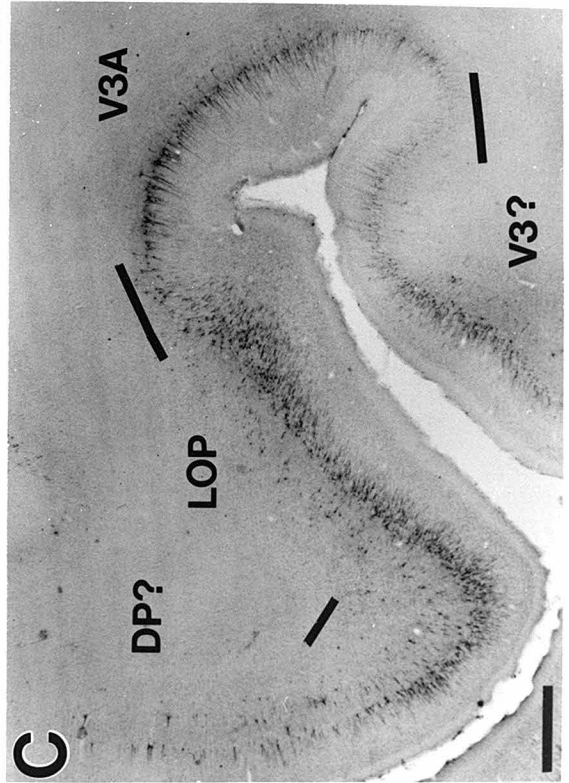
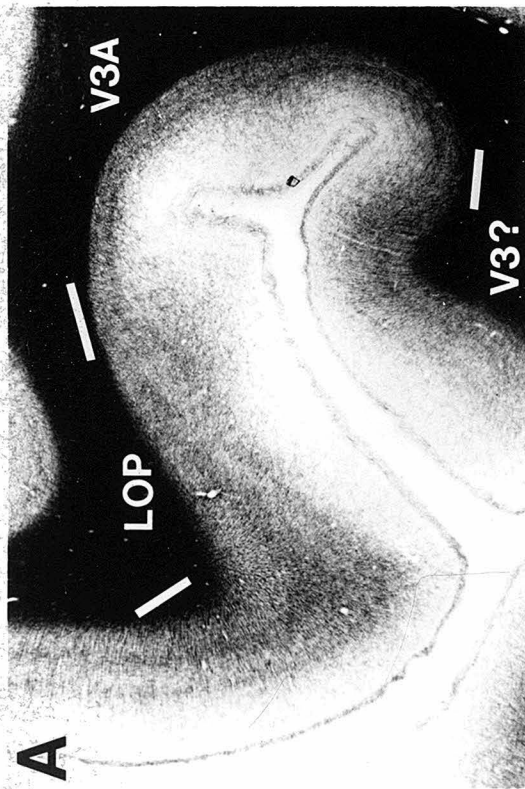
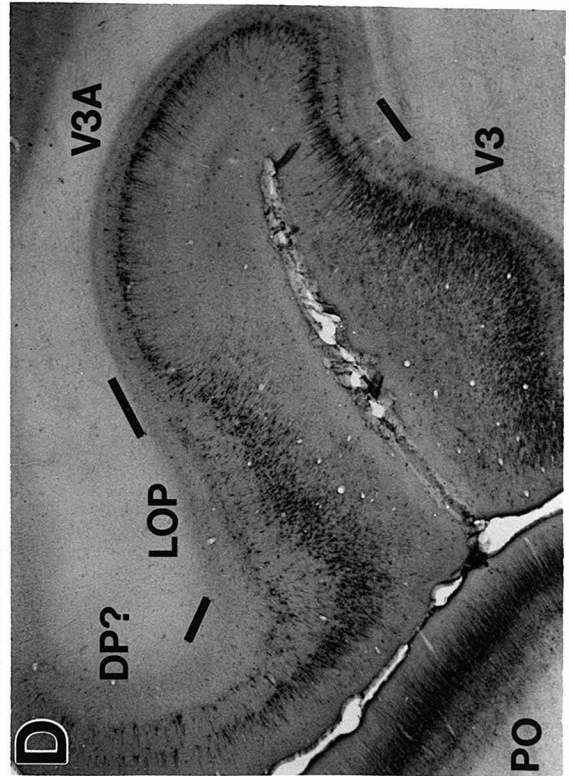
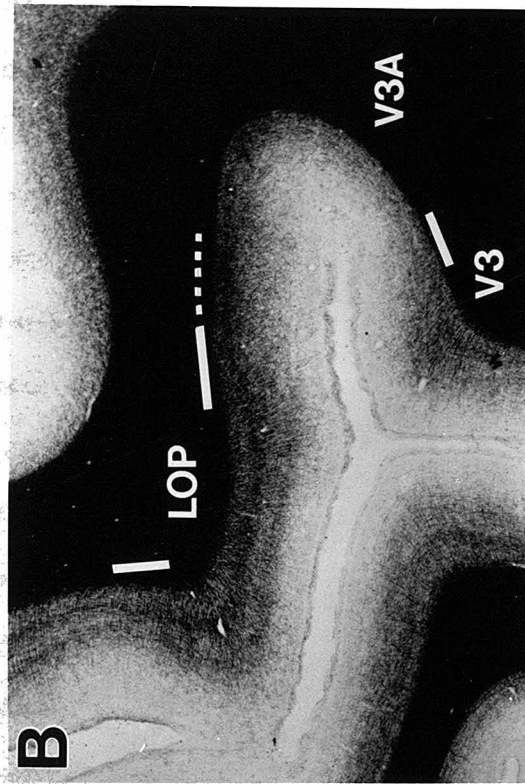
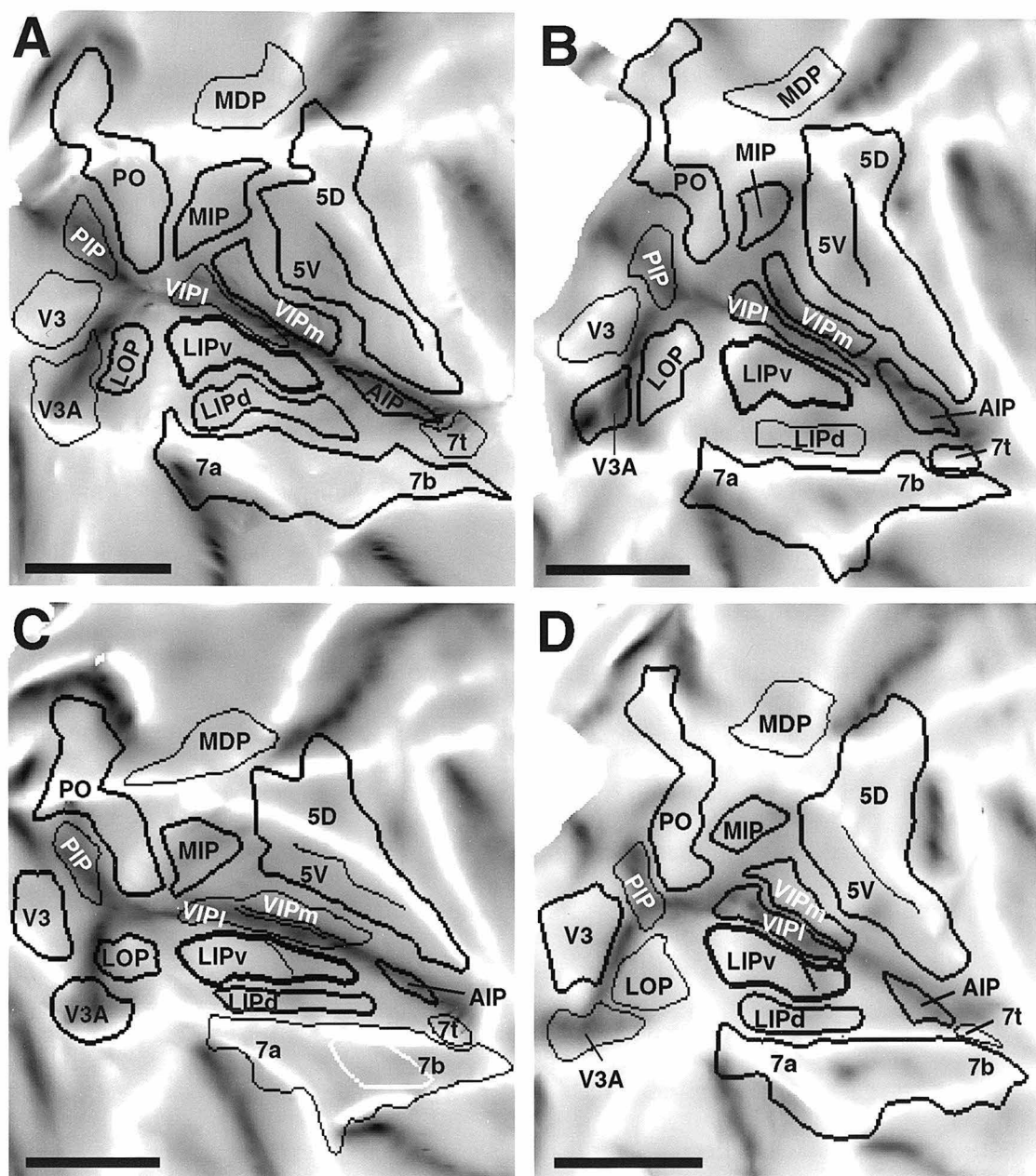


Figure 10. Flat map representations of the distribution of architectonic areas of and near the IPS, illustrating variability from four hemispheres. (A) Case 95DR (right hemisphere), coronal plane of section. (B) Case 95DL (left hemisphere of the case in panel A, oriented as a right hemisphere, coronal plane of section. (C) Case 94CR, coronal plane of section. (D) Case 93IR, coronal-sagittal plane of section. The white outline in 7a/7b indicates compromised tissue. Other conventions as in Figures 2 and 3. Scale bars equal 1 map-cm.



subdivision boundary (panel C). The location of the VIPm/5V border ranged from 2 to 5 mm up the medial bank, and VIPl/LIPv border ranged from 1 to 2 mm up the lateral bank. Additionally, connectivity patterns support our designation for the VIPm/5V architectonic boundary (Chapter 3).

Along the length of the IPS fundus, the distinguishing architectonic features between areas PIP, VIPl and AIP were subtle, being distinguished by both the laminar and radial organization of myelination and SMI-32-ir cell label (Figs. 1, 4, and 6). These subtleties are reflected by the relatively large transition regions between these areas. Together, these three areas overlap much of IPd of Seltzer and Pandya (1986). The boundary between AIP and LIPd/LIPv was also subtle, having features intermediate between the three areas. This transition region (and possibly anterior portions of LIPd and LIPv) may constitute a separate zone, overlapping cortex involved with the visual guidance of hand movements (Taira et al., 1990).

Areas V3, V3A, PO, and zone LOP were variable in size and shape, which was related in part to the plane of sectioning and perhaps the irregular folding patterns in this portion of the hemisphere. Based on geography and previous studies, the total areal extent of V3, V3A, and PIP may be substantially greater than is depicted in the four hemispheres in Figure 10 (cf. Felleman and Van Essen, 1991). Colby et al., (1988) placed MDP bordering PO, whereas a large gap separated these two areas in the present study, especially along the medial wall. This zone along the wall overlaps 7m of Preuss and Goldman--Rakic, (1991b), and may constitute a separate area. Additionally, the gap between PO and MDP along the parieto-occipital sulcus may correspond to V6A of Galletti et al., (1996). The extent of zone 7t may generally be comparable in size to that shown in Figure 10A. However, in several cases, the architectonic characteristics of 7t gradually merged with area 5 medially and area 2

anteriorly, resulting in a relatively large transition region. Similar areal distributions of the seventeen regions in the IPS/POS region were observed in the remaining hemispheres of this study.

Architectonic maps of the cortical hemisphere

The architectonic parcellation of much of the right hemisphere of case 95DR is represented in three complementary display formats: a series of coronal sections (Figure 11), a cortical flat map (Figure 12), and a three-dimensional reconstruction (Figure 13). The coronal series is better suited for directly comparing boundaries with previous studies that used the same plane of sectioning. The section-by-section representation better preserves the relative three-dimensional positions of areas, but it also illustrates the difficulty of appreciating spatial relationships across sections. The three-dimensional reconstruction is useful for appreciating the overall layout of area, but many areas are obscured by cortical folds. The drawbacks of these two representations makes clear the complementary advantages of a flat map representation of all the data on a single display.

In Figure 11, the top left inset shows a lateral view of the 3D reconstruction of case 95DR, indicating the location of 10 (out of 95) coronal sections from this cortical block that are illustrated in the figure (panels A - J). The lower left inset shows the location of the same 10 layer 4 contours on the flat map (architectonic borders were omitted for clarity; also see Fig. 2E). In sections A through J, architectonic transition regions are indicated by shading along the cortical ribbon, and cortical areas and regions of uncertainty ('?') are indicated. In some sections, transitions between regions of uncertainty were indicated (i.e., panel I along the STS), though do not

appear on the other map reconstructions. The span of the transition regions typically ranged from 1 to 3 mm, though varied from 0.5 mm (such as the V1/V2 border in panel A) to 6 mm in regions where the cortex was sectioned very obliquely (such as the posterior arcuate region in panel H).

Figure 12 shows the parcellation of case 95DR on a flat map including 79 areas and zones (labels). As observed earlier with areas of the IPS, the majority of core regions have elongated axes, most of which run parallel to the nearest sulcal fold. The primary somatosensory strip, areas 1, 2, 3a, and 3b, are extreme examples of this, each extending along the posterior bank of the central sulcus along the posterior ridge, as noted in previous studies (cf. Pons et al., 1985). Several areas were identified as being particularly robust in architecture in this case (heavy outlines), including areas LIPv, MT, entorhinal cortex (ER), the auditory complex (A1/R), gustatory cortex (G), 45, and a portion of the S2 complex. Along the medial and lateral extents of primary somatosensory cortex (areas 3a, 3b, 1, and 2), a line is drawn indicating a sharp and robust SMI-32-ir cell label transition that may represent the full extent of primary somatosensory cortex. However, the individual areas could not be distinguished in this region.

The locations of 5 areas were estimated primarily on geography, relative to previous physiological and anatomical mapping studies, including areas VP (Burkhalter et al., 1986; Newsome et al., 1986; Felleman et al., 1997), VOT (Felleman et al., 1986), DP (May and Andersen, 1986), area 31 (Vogt et al., 1987) and portions of the S2 complex outside the two core regions of S2 (Burton et al., 1995). Some portions of the reconstruction, such as the anterior temporal pole, were not mapped in this hemisphere even though published architectonic criteria do exist (Jones and Burton, 1976; Seltzer and Pandya, 1978; Amaral et al., 1987; Saleem and Tanaka, 1996).

Before discussing the subset of areas meriting specific comment, we first illustrate architectonic maps from two additional cases, which are shown in Figures 14 and 15. All three flat maps are similar to one another and to previously published flat maps in their basic layout and internal geography (Van Essen and Maunsell, 1980; Drury et al., 1996a). However, there are moderate differences in the overall shapes relative to the extent of cortex included in the representation (dimensions of the original cortical block), and in the size and shape of various sulci. The anterior boundary was defined by the anterior-most coronal section of each block (different for every case).

The sulcal patterns evident in the curvature maps in Figures 12, 13, and 14 (2D and 3D maps) were grossly in register, but show modest variability in the depths and size of buried cortical regions. The differences in sulcal patterns across each hemisphere in the flat maps were primarily related to animal variability, though some of the variability resulted from the flattening process, especially near the edges of the map where the cortex can be expanded. Figure 13 (case 94CR) included the largest expanse of cortex, containing several prefrontal areas (Carmichael and Price, 1994).

Figure 11. Illustration of architectonic core regions on coronal sections from case 95DR. Top left inset shows a lateral view of the 3D layer 4 reconstruction, indicating the location of the coronal sections, spaced 2.9 mm apart. Middle left inset shows the corresponding flat map indicating the location of the layer 4 section contours. Panels A through J illustrate coronal sections indicating areas and zones (labels) and transition regions (shaded). In section D, ss = primary somatosensory cortex. Scale cross is 1 map-cm, and scale bar is 1 cm. Other conventions as in Figure 2.

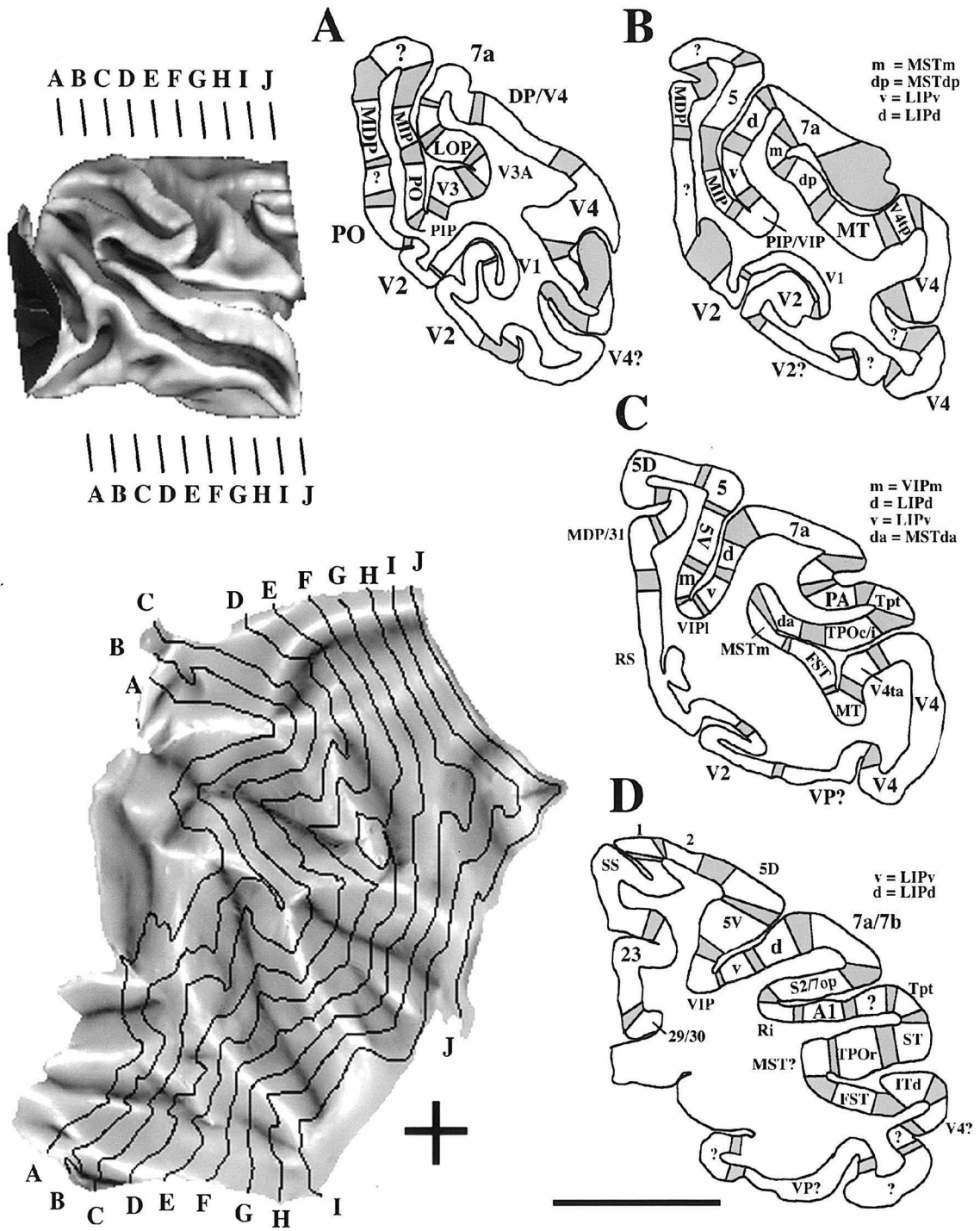


Figure 11 continued. Coronal sections from case 95DR showing areas and zones (labels) and transition regions (shaded). Scale is 1 cm.

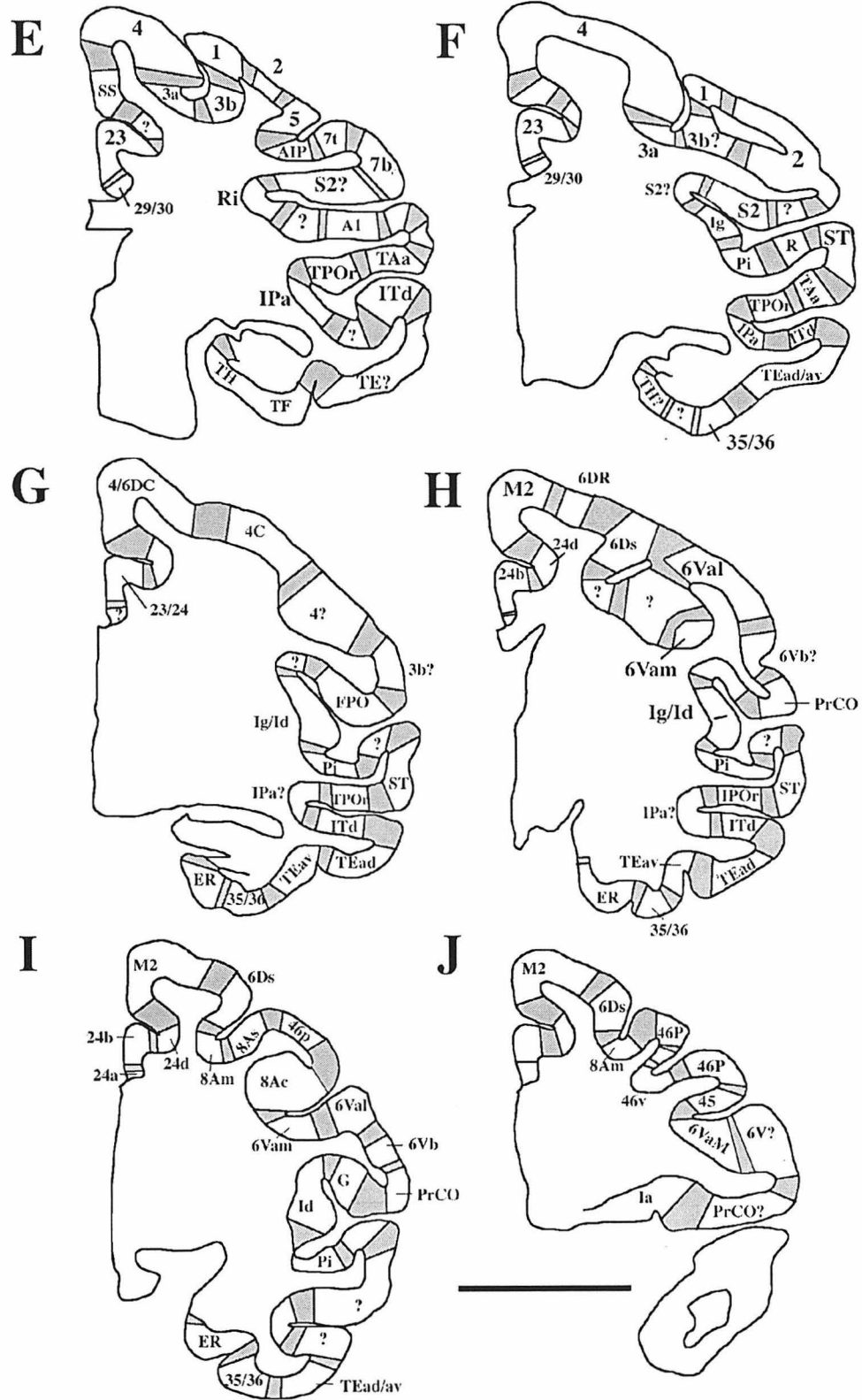
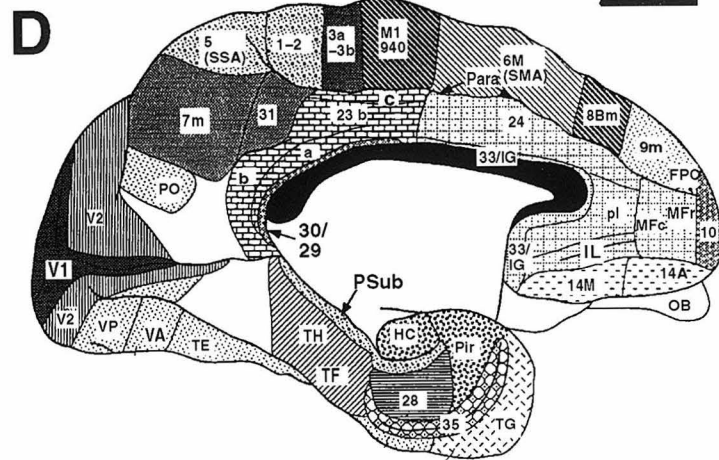
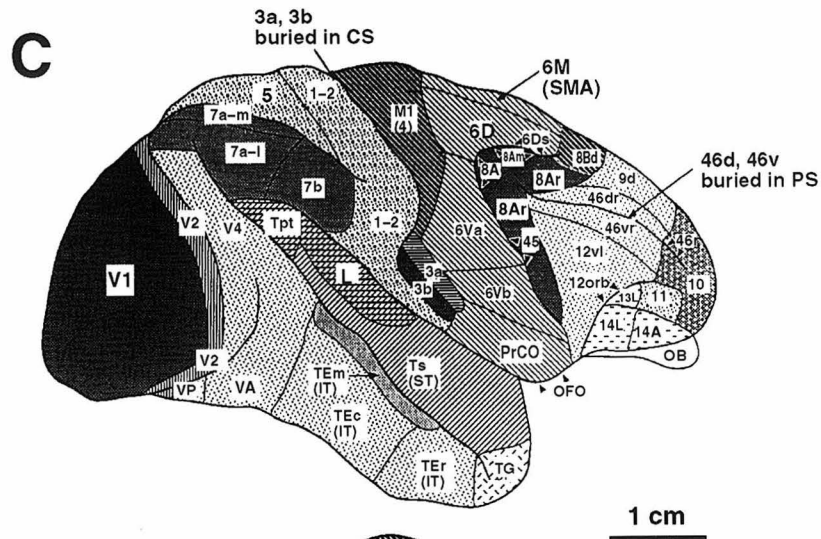
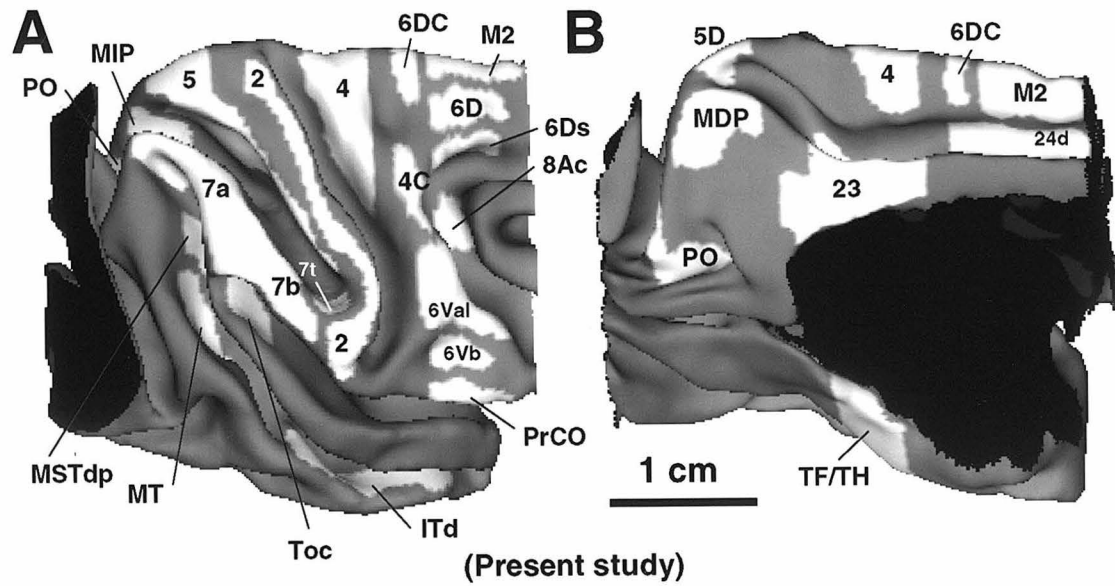


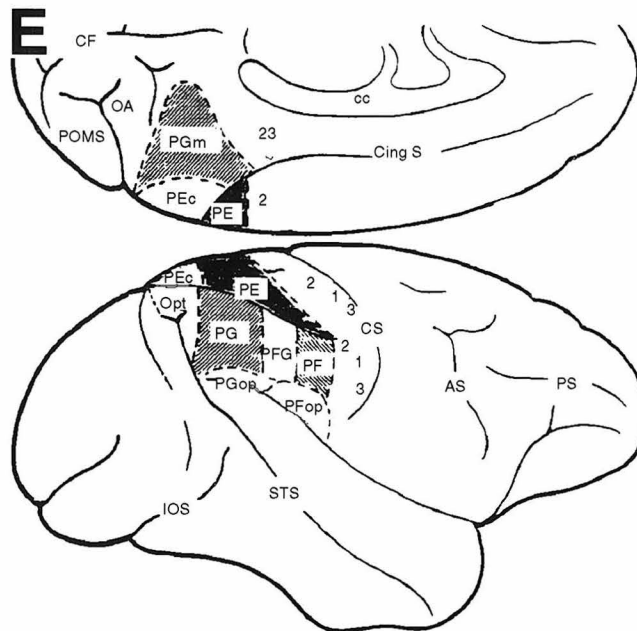
Figure 12. A flat map representation of case 95DR including 79 architectonically derived areas and zones embedded in the curvature map. Areas or zones that extend beyond the bounds of the flat map are indicated by open contours. The two light gray encircled regions overlapping portions of 7a/7b and the V4/DP/MT transition region represent cortical tissue that was compromised by skull openings (resulting from tracer injection experiments). The insets show a lateral and medial view of the portion of the reconstructed hemisphere (layer 4 surface) that is present in the flat map. Area V1 and portions of the frontal lobe and the temporal pole are not included in the map. To further reduce surface distortions, one cut was introduced (dashed lines) extending from V1, along prestriate cortex, and out to the corpus callosum. In the superior temporal sulcus, m = MSTm, dp = MSTdp, da = MSTda, and i = TPOi. Scale cross is 1 map-cm, and applies to all panels.

Figure 13. Three-dimensional reconstruction of case 95DR illustrating a subset of the areas and zones identified in the present study, and parcellation schemes from other studies (A-K). (A, B) lateral and medial view of case 95DR of the present study, illustrating the 3D location of a subset of the areas in shown in Figures 11 and 12. (C, D) Parcellation from Preuss and Goldman-Rakic, (1991b) re-oriented to facilitate comparison with previous study. Scales are 1 cm.

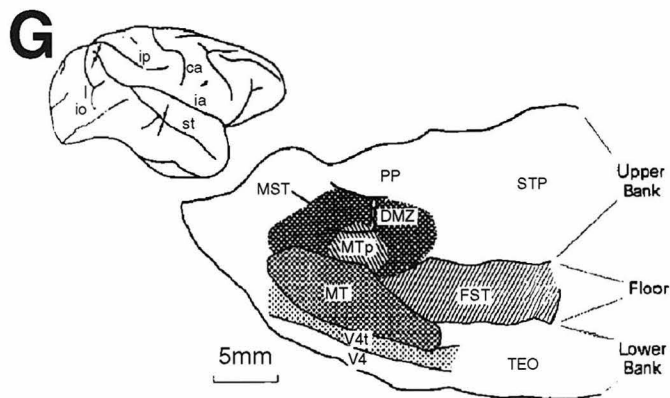


(Preuss and Goldman-Rakic, 1991b)

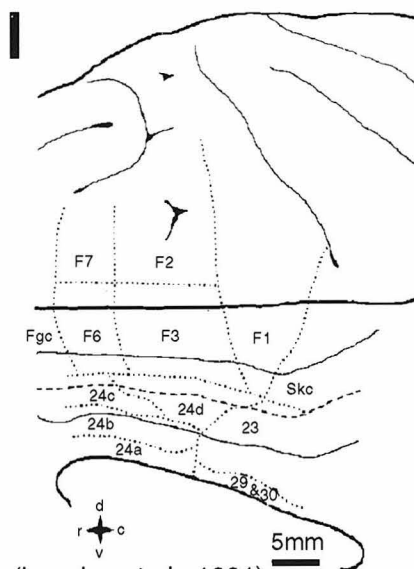
Figure 13 continued. Comparison with previous studies. (E) Pandya and Seltzer (1982) identified area PEc, which overlaps portions of MDP of the present study. PG and PF correspond to 7a and 7b, respectively, and their PGop may correspond to 7op. (F) The location of LIP and 7a plus 7b, and the estimated location of DP in the present study were adopted from Andersen et al., (1990). (G) Criteria for identifying areas FST, V4t, and the densely myelinated zone (DMZ) (which we termed MSTda) were from Desimone and Ungerleider (1986). (H) Definitions for TPO subdivisions and IPa were borrowed from Cusick et al., (1995). (I) Definitions of area 24 subdivisions were adopted from Luppino et al., (1991). (J) Areas M2 (MII), 6DC, 4C, 6Va (6Val) and 6Vb were borrowed from Barbas and Pandya (1987).



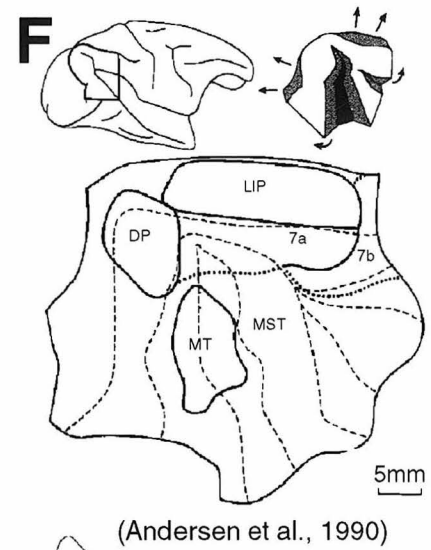
(Pandya and Seltzer, 1982)



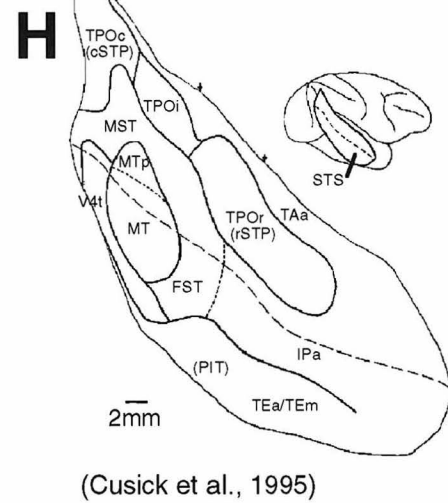
(Desimone and Ungerleider, 1986)



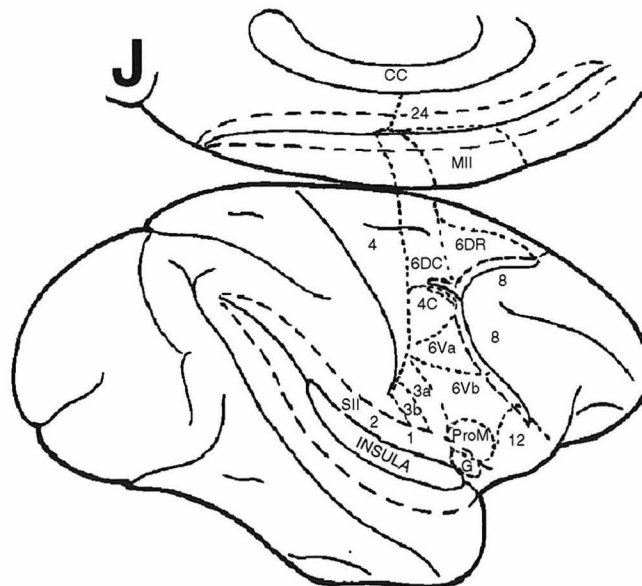
(Luppino et al., 1991)



(Andersen et al., 1990)

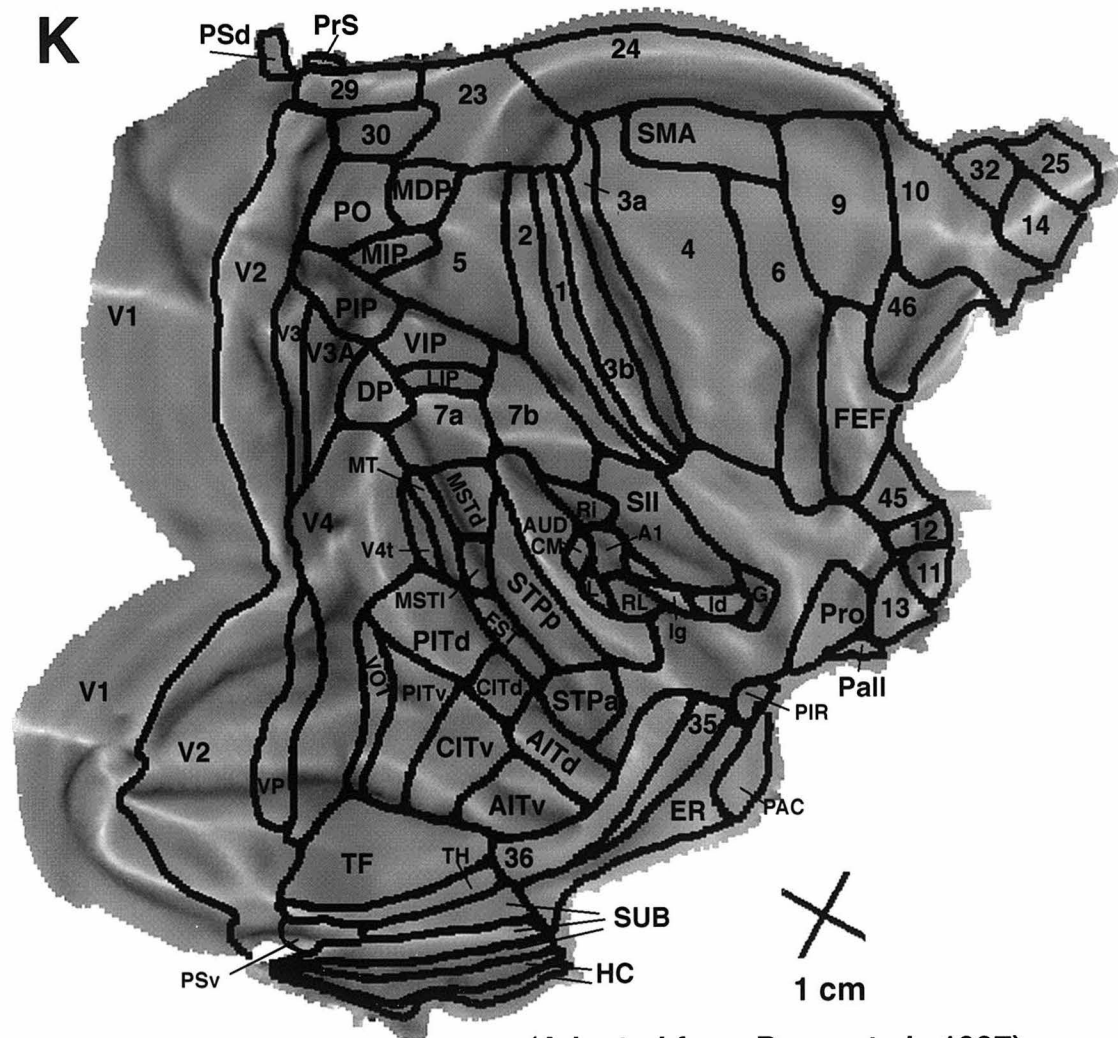


(Cusick et al., 1995)



(Barbas and Pandya, 1987)

Figure 13 continued. Comparison with previous studies. (K) Flat map adapted from Felleman and Van Essen, (1991) with permission. The map represents a summary parcellation of cortical areas based on architectonic as well as other criteria, and is superimposed on a map of sulcal curvature. The map was generated using the methods of the present study (cf. Figs. 12, 14 and 15).



(Adapted from Drury et al., 1997)

Figure 14. Flat map representation of case 94CR including 89 architectonically derived areas and regions (labels). Insets show the lateral and medial views of the extent of the cortical surface present in the flat map. Two cuts were introduced to reduce distortions. One extends from the V1/V2 border, along prestriate cortex, and anterior to the corpus callosum. The second extends from agranular insular cortex, along lateral prefrontal cortex (between areas 14 and 13b), and out to the anterior-most section of the block. The anterior-most section was tessellated in a manner that it completed the frontal pole, though more cortex was present beyond this section. Thus, areas 46v and 10m extend further into the crease in the upper right of the map, which differs from the other flat maps. Scale cross is 1 map-cm, and applies to all panels. Other conventions as in Figure 12.

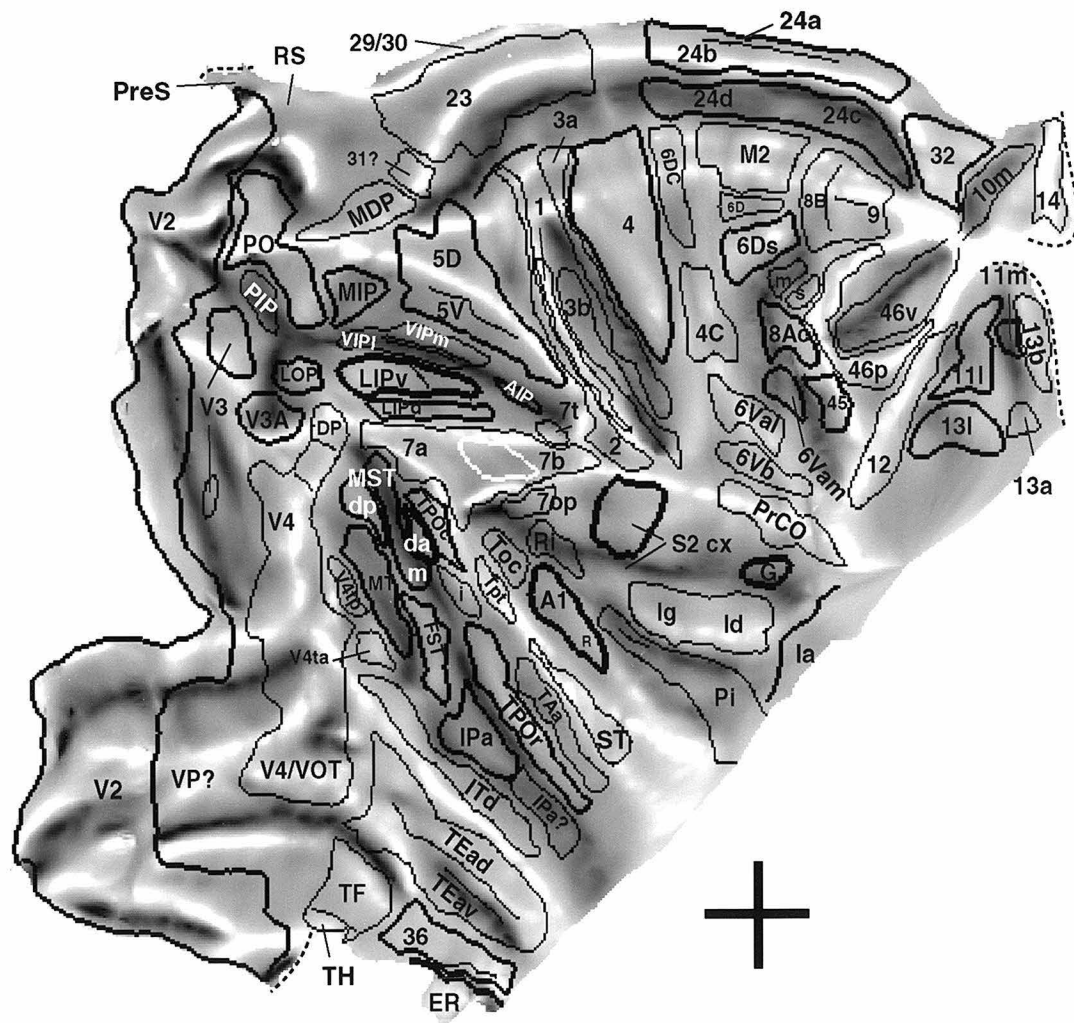
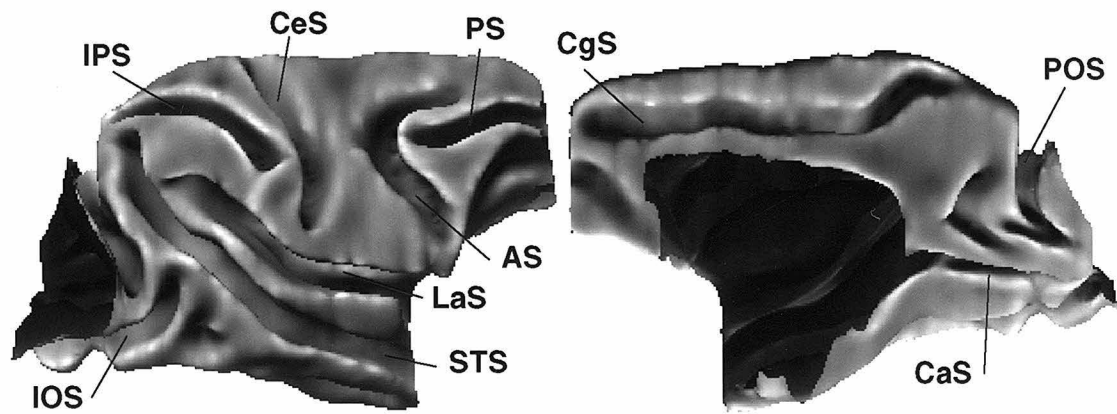


Figure 15. Flat map representation of case 93IR, showing 75

architectonically derived regions and areas. Much of the frontal lobe, the tip of the temporal pole, and the posterior-most portions of V2 were not included in the original cortical block. Two cuts were introduced, one extending from V1, along prestriate, and rostral to the corpus callosum, and the other extends from the callosum, along the architectonic border between 13b and 14, out to the anterior-most section of the block. The finger-like projection of medial prefrontal cortex results from its not being well constrained by cortex further rostral (as in Figure 13). The pre- and post-central dimples, as well as minor misalignment "ripples", are more evident in this case than the previous two (Figs. 12 and 13). Scale cross is 1 map-cm, and applies to all panels. Other conventions as in Figure 12.

Parcellation of the cortical hemisphere

Several previous studies have described architectonic parcellations of the entire (or large portions) of the cerebral hemisphere of the macaque (Brodmann, 1909; von Bonin and Bailey, 1947; Preuss and Goldman-Rakic, 1991a,b), and numerous additional studies have focused on the architecture of more restricted regions of cortex, some of which are illustrated in Figure 13. The architectonic criteria we found most reliable come from these or other studies, depending on the region. Here, we discuss mainly areas and zones where our analysis suggested a refinement or revision of existing schemes in the temporal and frontal lobes.

Temporal cortex. The STS contains mainly visual areas on its ventral bank, and polysensory areas on its dorsal bank. Within the STS, we largely followed the nomenclature and architectonic criteria described by Cusick et al., (1995) (Fig. 13H) and Desimone and Ungerleider (1986) (Fig. 13G), with the exception of a revised scheme for the MST complex, V4t, and zone ITd (also see Baylis et al., 1987). Different schemes have been used to parcel MST based on physiological criteria, but also on grounds of architecture and connectivity (Desimone and Ungerleider, 1986; Komatsu and Wurtz, 1988; Seltzer and Pandya, 1989; Boussaoud et al., 1990). In addition to the architectonic subdivisions FST and the densely myelinated zone of Desimone and Ungerleider (1986) (termed MSTda in this study) we identified a zone that we call MSTdp (dorso-posterior subdivision). Figure 16 shows the architecture of this area in the posterior STS from case 93IR. In panel A, the subdivision MSTdp was distinguished from MT in myelination by its slightly less dense and less matted appearance (Van Essen et al., 1980). Additionally, in most cases, MSTdp showed a more visible

bilaminar organization and radial component than MT. In panel B, area MT showed an organized trilaminar appearance in SMI-32-ir cell label including layers 3, 5, and 6 (Cusick et al., 1995; Hof and Morrison, 1995). The pattern in MT was similar to that of MSTdp, except that in MT the layer 3 band was often broader and layer 6 was more distinct, giving MT an overall more organized appearance. The MT/MSTdp architectonic boundary was further supported by connectivity patterns (Chapter 3).

Figure 15 also illustrates the transition from MSTdp to MSTm (medial), which is characterized by a marked decrease in myelination and SMI-32-ir cell label near the medial fundus. MSTm occupied the superior fundus of the STS, containing a single band of myelinated fibers spanning layers 3 through 6, and a relatively thin band of SMI-32-ir cell label in layer 3. The staining of MSTm was variable, in part due to sulcal curvature. Outside of MSTda (the densely myelinated zone), the degree of correlation between physiological boundaries of MST subdivisions in previous studies and our architectonic boundaries is not clear.

In Figure 16B, area 7a shows a very light SMI-32-ir cell label (upper left corner of panel). Similarly, area V4 was also very lightly stained, showing a thin, distinctive band of label in layer 3. The staining features of these two areas were consistent in 7 hemispheres examined with this antibody, yet differed significantly from the description of Hof and Morrison (1995). The location of V4 and 7a were also identified based on myeloarchitecture (cf. Colby et al., 1988; Preuss and Goldman-Rakic, 1991b). Area V4t contained myelination and SMI-32-ir cell label intermediate between areas V4 and MT, consistent with other studies (Desimone and Ungerleider, 1986; Hof and Morrison, 1995). However, V4t showed modularity in SMI-32-ir cell label and myelination, and was divided into a posterior (V4tp) and anterior (V4ta)

subdivision. Zone V4ta (not shown) was distinguished from V4tp by heavier myelination with a stronger radial component, by denser SMI-32-ir cell label, and in Nissl stained sections by a denser band of pyramidal cells in layer 3. V4ta was more similar to ITd than V4tp in some cases, though geographically overlapped the location of V4t in the above studies.

In Figure 17, coronal sections through mid-portions of the ventral bank of the STS are shown, illustrating the zone ITd. ITd was best characterized by SMI-32-ir cell label (Fig. 16B), being distinguished from medial and lateral cortex by a dense population of SMI-32-ir cells in layer 3, and moderate cell density in layers 5 and 6 (Hegd  and Felleman, 1995). The lateral border of ITd was often striking, in that cortex ventral to the STS was very sparsely populated with SMI-32-ir cells. A posterior to anterior gradient of decreasing density in SMI-32-ir cell label was observed, though the lateral boundary was distinct and often striking throughout. In myelin sections, ITd was characterized by a moderate outer band and lighter inner band of Baillarger (Fig. 17A). Relative to medial area IPa, ITd showed a stronger radial component and was often more densely myelinated overall. The ventral ridge of the STS was variable in myelination (scored as a transition region), though often characterized by denser myelination. Area TEad (ventral to the lower lip of the STS) was characterized by dense inner and outer bands of Baillarger and a strong radial component, both of which correlated with the cytoarchitectonic border described by Saleem and Tanaka (1996). Note that the dense myelination of TEad corresponds with very light SMI-32-ir cell label, which is similar to the pattern observed for area 7b (Fig. 5). The dorsal border of TEad, did not coincide with the lateral SMI-32 border of ITd, leaving an intervening region labeled by a question mark (Fig. 17B). Similarly, the SMI-32-ir border did not coincide with the cytoarchitectonic boundaries of area TEm, located

Figure 16. Coronal sections from case (93IR) of posterior portions of the STS stained for myelinated fibers (**A**) and SMI-32-ir cells (**B**), illustrating areas MSTm and MSTdp, in addition to areas 7a, MT, V4tp, and V4. Panel A is of higher magnification than panel B. The m in panel B is MSTm. Panel scales are 1 mm, and inset scales are 1 cm.

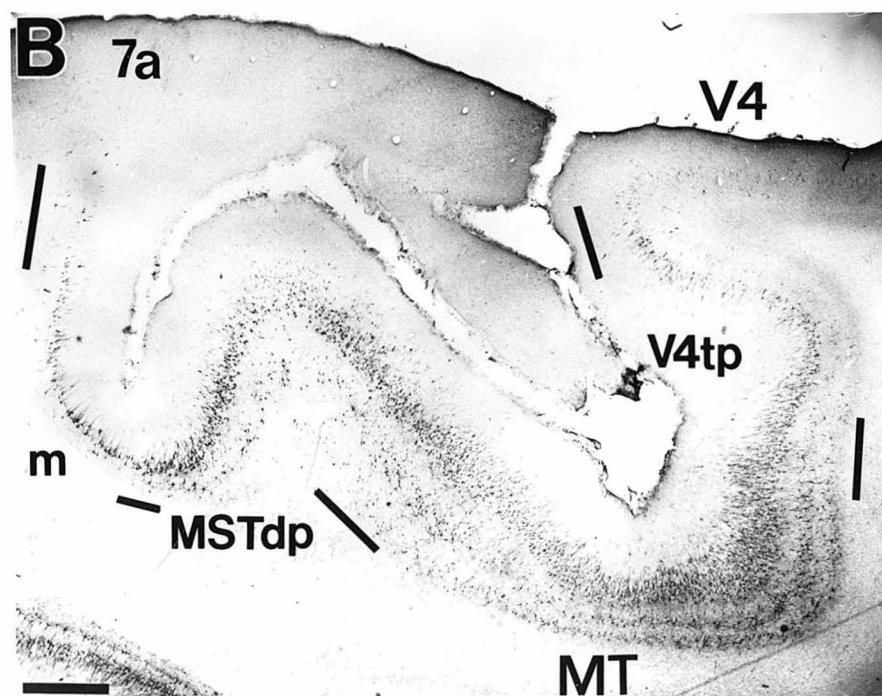
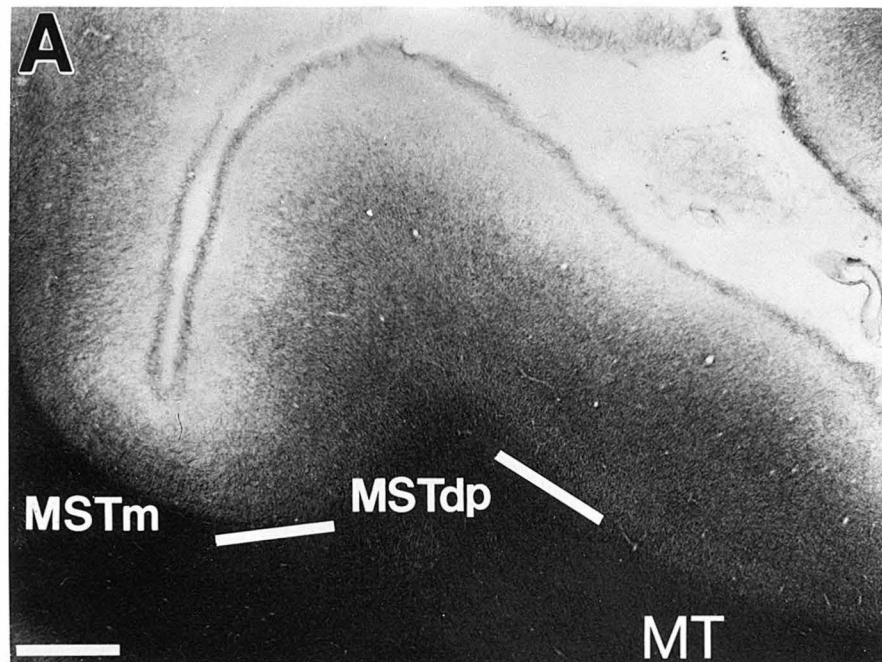
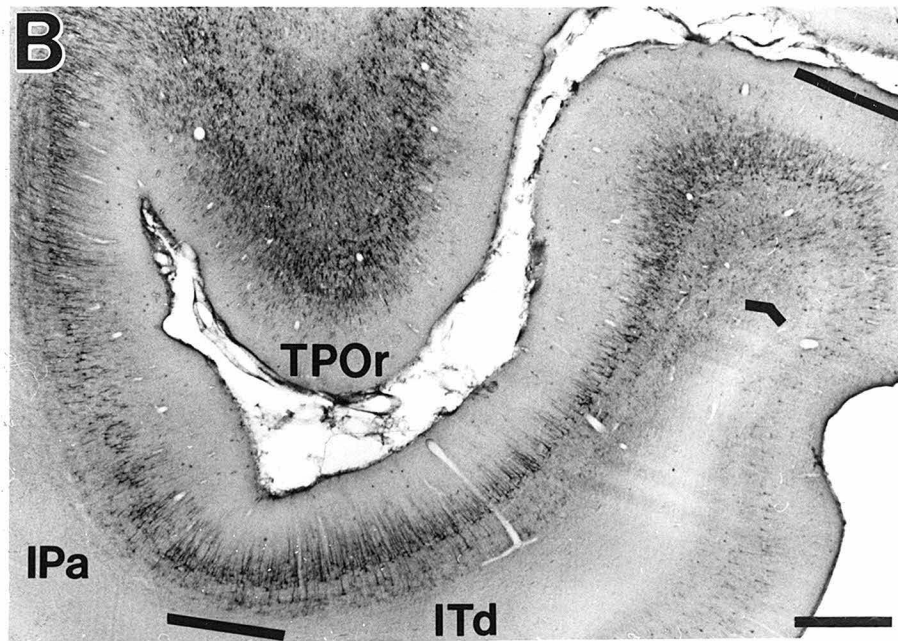
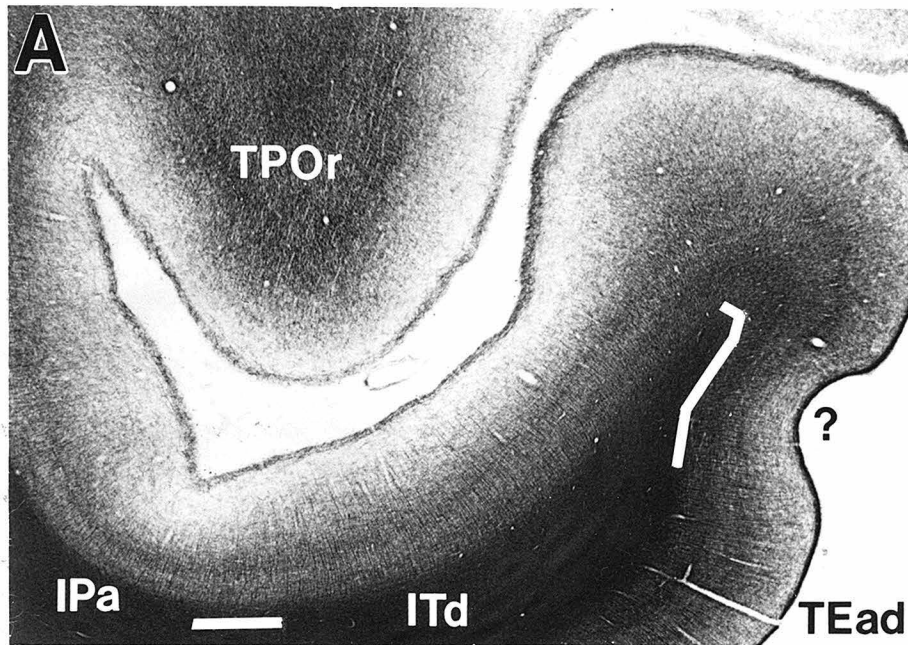
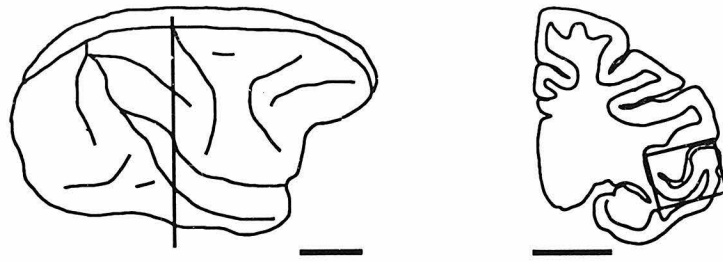


Figure 17. Coronal sections of case 93IR through the middle portion of the STS, and stained for myelinated fibers (A) and SMI-32-ir cells (B), illustrating the zone ITd, and areas IPa, TPOr, and TEad. Panel scale is 1 mm, and inset scales are 1 cm.



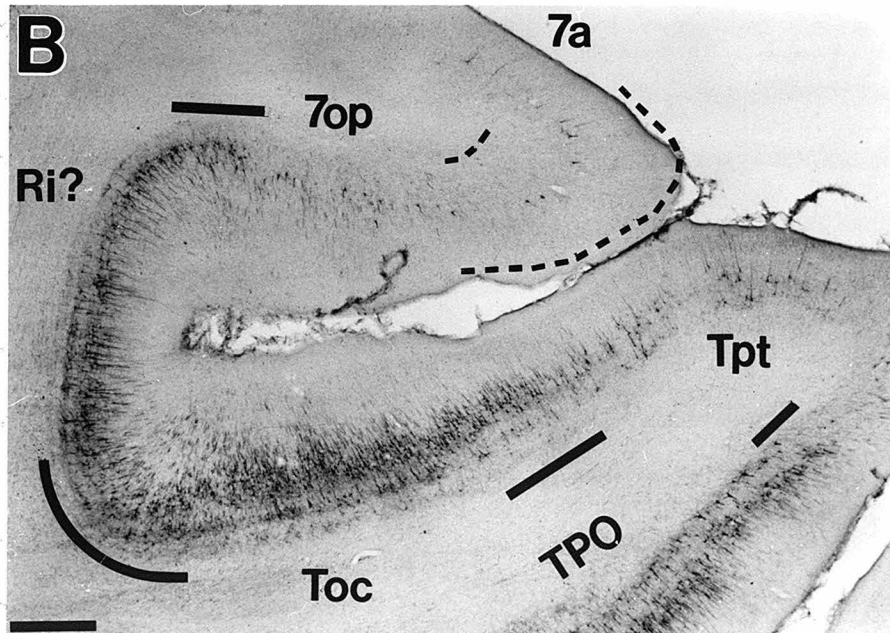
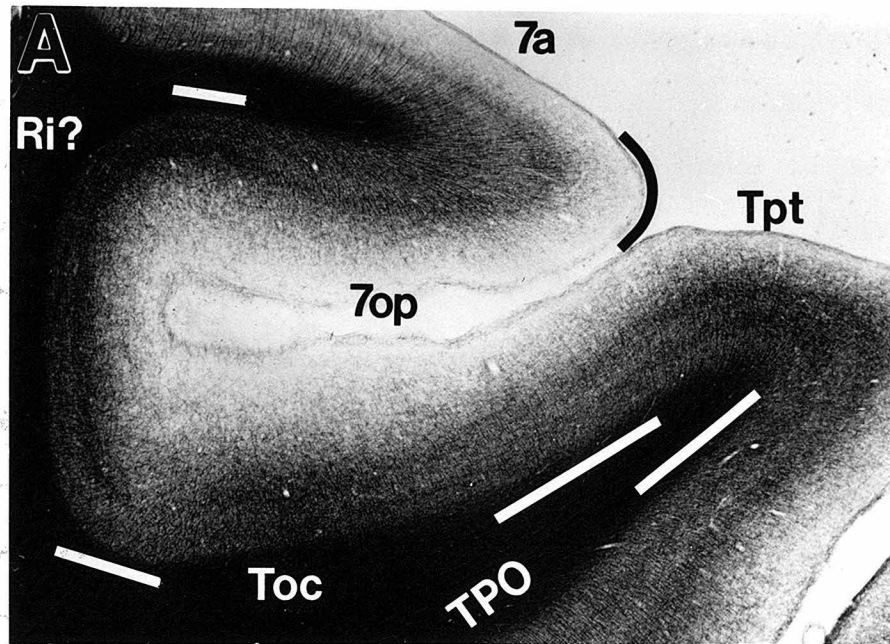
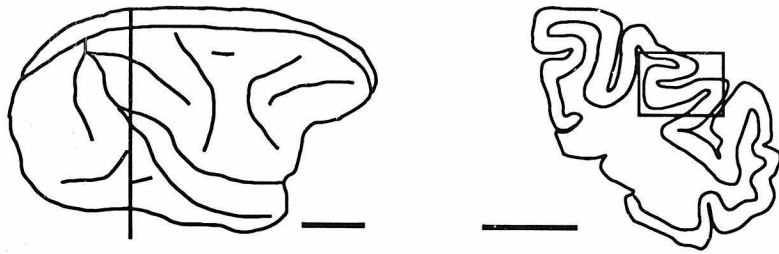
along the ventral rim, though TEm was not systematically mapped in the present study (Seltzer and Pandya, 1978; Preuss and Goldman-Rakic, 1991b).

Cortex lying ventral to the STS and along the ventral temporal lobe was parceled exclusively with cyto- and myeloarchitecture, as SMI-32-ir and CAT-301-ir cell label was very sparse, providing little or no differential label in our tissue. Areas identified in this study included TEad, TEav, 35, 36, and 28 (entorhinal cortex, ER) (Saleem and Tanaka, 1996; also see Amaral et al., 1987), and areas TF and TH (Seltzer and Pandya, 1976).

Lateral sulcus. We mainly used the criteria described by the following authors for the lateral sulcus: Preuss and Goldman-Rakic (1991b) for areas 7op, Tpt, and PrCO; Jones and Burton (1976) and Friedman et al., (1986) for areas S2, Ri, Pi, and the insular regions Ig, Id, and Ia; Morel et al., (1993) for areas A1 and R; and Carmichael and Price (1994) for gustatory cortex (G). As illustrated in Figure 18, zone Toc (temporal opercular, caudal) represents a revision of what we interpreted to be auditory area C (caudal to A1) of Morel et al., (1993), and of area T3 as revised by Akbarian et al., (1994). Zone Toc is best distinguished by SMI-32-ir cell label, which was dense along the ventral bank of the lateral sulcus, including a broad band of label in layer 3, a thin band in layer 5, and sometimes a lighter band in layer 6. This pattern was similar to that in A1, though not as dense. In myelin, Toc had an overall dense and matted appearance, in contrast with the more distinct banded patterns of cortex medial (Ri) and lateral (Tpt). Zone Toc may overlap portions of Tpt and Ri defined by Preuss and Goldman-Rakic, (1991b).

Figure 18 also illustrates area Tpt, 7op, 7a, and possibly portions of the posterior portion of the retroinsular area (Ri). Area 7a had a stronger radial component than 7op, while 7op was characterized by a denser outer band of

Figure 18. Coronal section through the posterior portion of the lateral sulcus of case 93IR, stained for myelinated fibers (A) and SMI-32-ir cells (B), illustrating zone Toc. Also illustrated is the 7a/7b region and areas 7op, Ri, Tpt, and portions of TPO. Panel scale is 1 mm, and inset scales are 1 cm.



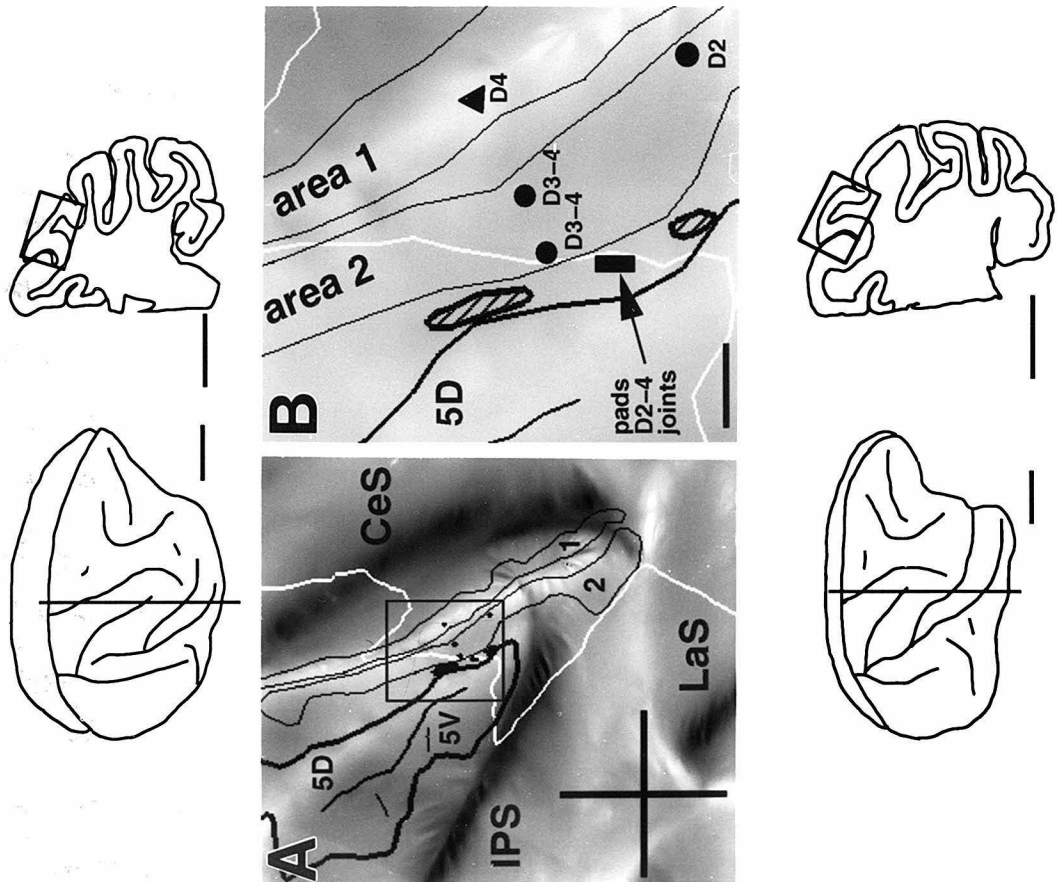
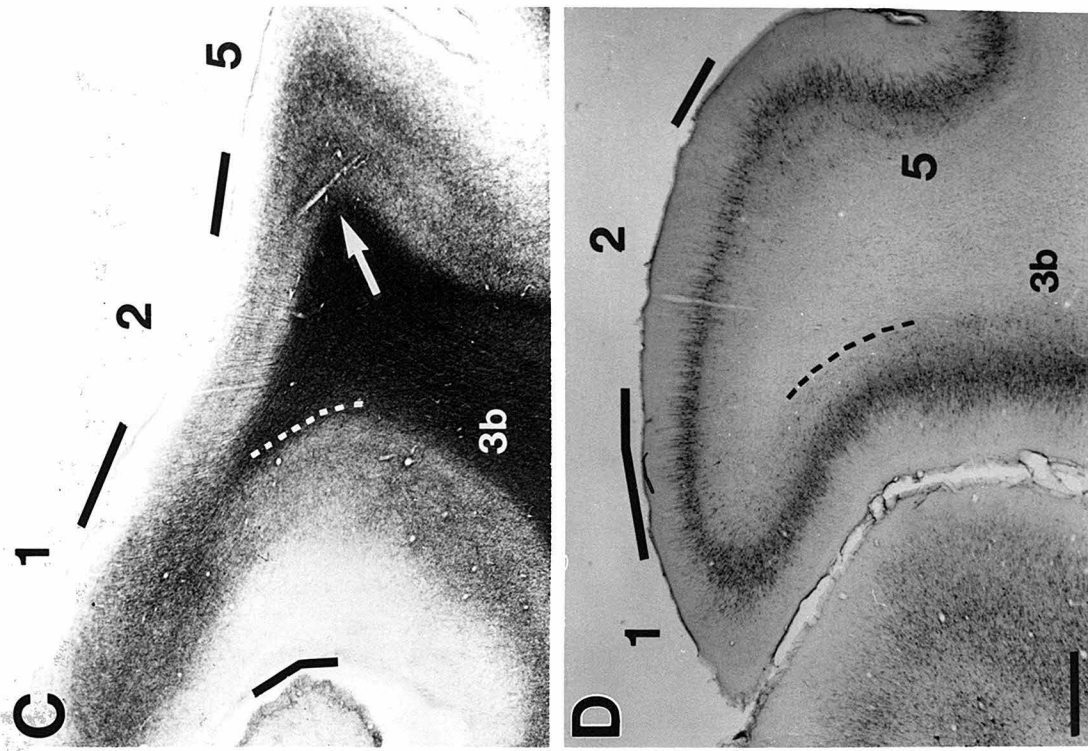
Baillarger. Additionally, SMI-32-ir label was sparser in 7a, gradually increasing in density in 7op. Area 7op was also identified in Nissl sections by its prominent band of layer 3 stained cells (Preuss and Goldman-Rakic, 1991b). Cortex along the fundus of the posterior lateral sulcus showed a slightly thinner band of myelination than surrounding cortex, including layers 3 through 6, which may correspond to be area Ri of Jones and Burton (1976). In Figure 18A, the myelination along the fundus was overall slightly denser and more banded in appearance than portions of area Ri further anterior, and thus was scored as uncertain in this section. Additionally, SMI-32-ir cell label in this region was intermediate between 7op and Toc, having moderate label in layer 3. Area Tpt was characterized by a stronger radial component in myelination, which corresponded with the radial columns in Nissl stains described by Preuss and Goldman-Rakic, 1991b). Tpt was also characterized by lighter SMI-32-ir cell label than Toc and TPO (TPOc and TPOi).

Somatosensory cortex. The architectonic criteria for delineating somatosensory areas were derived mainly from cytoarchitectonic and myeloarchitectonic features, including areas 3a, 3b, 1, 2, 5 (Jones et al., 1978; Pons et al., 1985), and 7b (PF), 7op (PFop), and visual-related area 7a (PG) (Pandya and Seltzer, 1982), and S2 (cf. Preuss and Goldman-Rakic, 1991b). SMI-32-ir cell label patterns provided additional useful criteria for delineating many of these areas, and one significant revision in this study concerns the posterior border of area 2. In three hemispheres, the digits and/or face representation of areas 1 and 2 was mapped physiologically near the tip of IPS. The architectonic characteristics in the vicinity of the physiologically defined region of area 2 were then used to chart the remaining boundaries of area 2.

Figure 19 illustrates the architectonic and physiological borders of somatosensory areas near the tip of the IPS. Panel A shows the recording sites for case 95DR on a flat map in relation to several major sulci and the core outlines of architectonically defined areas 1, 2, and 5 (also see Fig 12). An expanded view of the boxed region is shown in Panel B, which illustrates the location of the tactile receptive fields for five penetrations (and two microlesions). The triangle denotes properties characteristic of area 1 (strong cutaneous responses), circles denote properties defining area 2 (deep touch, little or no cutaneous responses), and the rectangle denotes response properties different from area 1 or 2 (joint movement, larger receptive fields), (Pons et al., 1985; Burton and Fabri, 1995). The white contour in panels A and B represent the location of the layer 4 contour of the myelin stained section illustrated in panel C, and the rectangle corresponds to the electrode track in panel C (arrow). In myelin stained sections, area 2 was moderately dense overall and was characterized by prominent radial fibers and sometimes bundles of fibers. Area 5 showed broader and denser inner and outer bands of Baillarger, with much less of a radial component, especially for cortex situated along a gyral ridge. Area 1 also showed denser myelination than area 2, and in this section showed fused bands spanning layers 3 through 6. However, in other sections, a separation between bands in area 1 was evident.

Panel D shows the SMI-32-ir cell label of a coronal section from a different case (93IR) taken from a similar location to that shown in panel C. Area 2 was characterized by a relatively thin band of medium sized pyramidal cells in layer 3, and in some sections a sparsely populated band of cells in layer 5 that included medium to large pyramidal cells (not shown). The lighter band of layer 3 SMI-32-ir cell label correlated well with the lighter myelination of area 2. The cytoarchitectonic borders of area 1 and 2 (not shown) were also

Figure 19. Physiological and architectonic delineation of areas 1 and 2. (A) Flat map including portions of the IPS, central sulcus (CeS), and lateral sulcus (LaS) of case 95DR. Scale is 1 map-cm. (B) Expanded view of the recording site near the tip of the IPS, showing the location five electrode penetrations. Hatched regions represent microlesions placed immediately posterior to the physiological boundary of area 2. Scale is 1 map-mm. (C) Coronal section stained for myelinated fibers from case 95DR, corresponding to the layer 4 contour in panels A and B. (D) Coronal section from case 93IR illustrating SMI-32-ir cell label characteristic of areas 1, 2, and 5 (and 3b). Cortex exposed during the recording procedure tended to be compromised for SMI-32 immunohistology, which is why a different case is presented. Scale is 1 mm and also applies to panel C. Upper left inset shows the location of the section in C and contours in A and B. Lower left inset corresponds to panel D. Inset scales are 1 cm.



consistent with the SMI-32 borders, though generally more subtle (Pons et al., 1985). The architectonic boundaries of areas 1, 2, and 5 (or presumed area 5) correlated with physiologically derived borders in the two other cases, and were similar in areal extent relative to the tip of the IPS.

The architectonic and physiological boundaries for area 2 in this study did not include the medial bank of the IPS, as it has in some studies (cf. Pons et al., 1985). Instead, the medial ridge of the IPS was characterized by a thicker band of SMI-32-ir cells in layer 3, and often denser myelination, which was not observed in physiologically identified portions of area 2. The architecture along the medial ridge was similar to posterior portions of area 5, though generally scored as uncertain due to artifacts related to sulcal folding.

The outline of somatosensory area 5 (Fig. 12) showed heterogeneity in myelination and SMI-32-ir cell label (Figs. 1, 6, 8) as well as cytoarchitecture and CAT-301-ir cell label (not shown). The subdivision 5V was restricted to cortex containing two clearly separated bands of Baillarger that were moderate in density overall, and is likely to correspond to PEa Pandya and Seltzer, (1982), though the criteria used were different. Also, PEa appears to extend further posterior in the IPS, overlapping area MIP of this study. Zone 5D represents the remaining portion of area 5 defined by cytoarchitecture, and is likely to be further subdivided as in previous studies (Vogt and Vogt, 1919; Pandya and Seltzer, 1982).

Premotor and prefrontal cortex. Regions of premotor cortex adopted in this study included cytoarchitectonically defined areas M2 and 4C of Barbas and Pandya, (1987) (Fig. 13J), and myeloarchitectonically defined areas 6Ds, 6D, 6Va (plus revised medial and lateral subdivisions), 6Vb, and PrCO of Preuss and Goldman-Rakic, (1991a) (Fig. 13C). In prefrontal cortex, we adopted

architectonic definitions for areas 8Ac, 8Am, 9, 46p (8Ar plus 46dr and 46vr), and 46v of Preuss and Goldman-Rakic, (1991a), and areas 45, 10, 11, 12, 13, 14, and 32 of Carmichael and Price (1994). Figure 20 illustrates areas 45, and zones 6Vam and 6Val. Area 45 is located along the ventral limb of the arcuate sulcus, occupying the shoulder and medial bank, and was characterized by relatively heavy myelination with a broad and dense outer band (Panel A), while in showing a corresponding increased density of SMI-32-ir cell label (Panel B). Area 45 in this study overlaps area 45 and possibly portions of area 8 of Carmichael and Price, (1994), with the 45/6Vam transition region overlapping area 8. Area 6Vam lies along the fundus of the ventral arcuate limb, and was characterized by very light myelination, and often a thin outer band, in addition to very sparse SMI-32-ir label. The medial 6Va subdivision was proposed by Preuss and Goldman-Rakic, (1991a), though not explicitly demarcated in their illustrations. 6Vam may correspond to area 45b of Schall et al., (1995).

The zone 6Val was more densely myelinated than 6Vam, having a more prominent outer band of Baillarger than surrounding cortex (Preuss and Goldman-Rakic, 1991a). In sections further posterior, the density of myelination and SMI-32-ir cell label of 6Val was typically greater than that shown in Figure 20. Zone 6Val may overlap subdivisions, such as F4 and F5 of Matelli et al., (1985), which are distinguished primarily by differential cytochrome oxidase staining.

The location of zone 6Vam (45b) and portions of area 45 (45a) may correspond to the lateral frontal eye field (FEFl) of Schall et al., (1995), while area 8Ac, and possibly portions of 8Am and 8As may correspond to their medial frontal eye field (FEFm). If so, it would indicate that both FEFl and FEFm

Figure 20. Coronal sections through the arcuate sulcus of case 94IR stained for myelination (A) and SMI-32-ir cells (B), illustrating zone 6Vam, 6Val, and area 45. Panel scale is 1 mm, and inset scales are 1 cm.

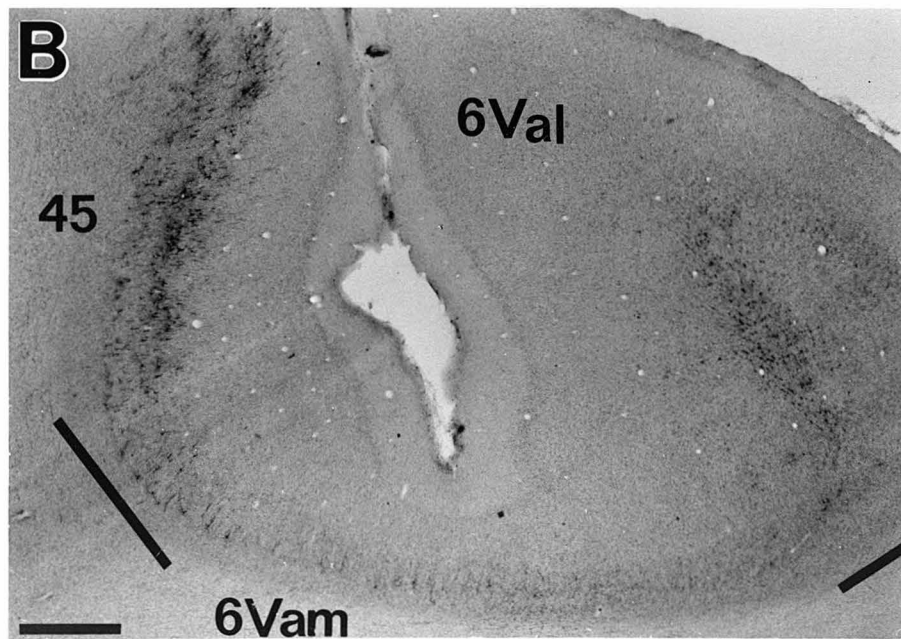
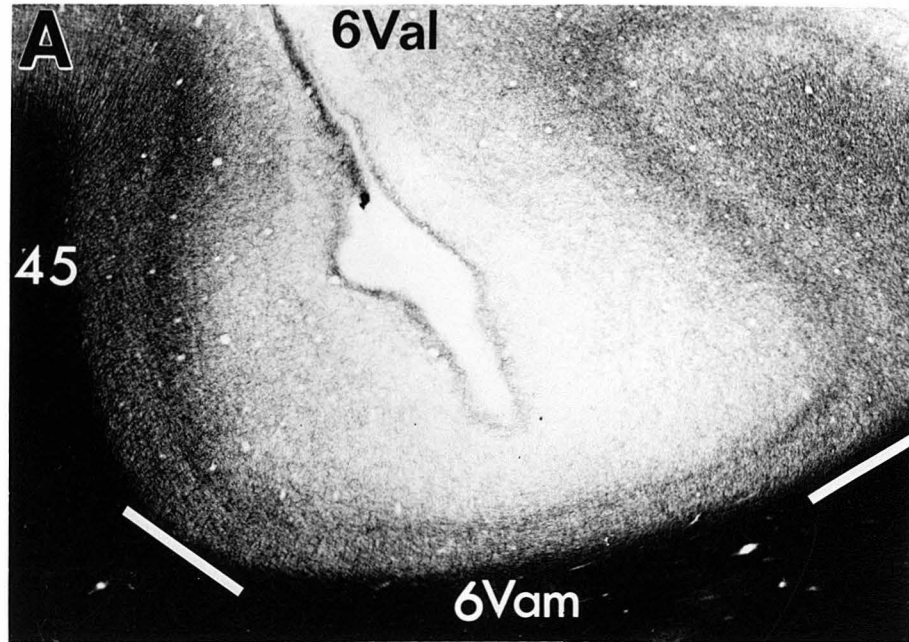
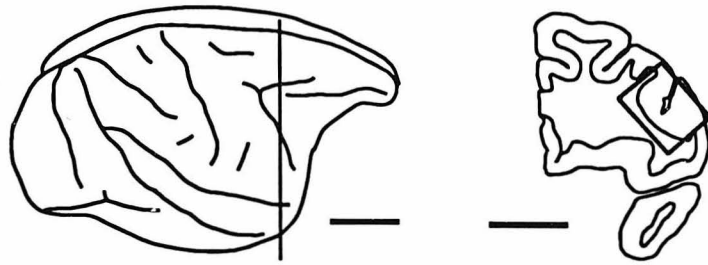
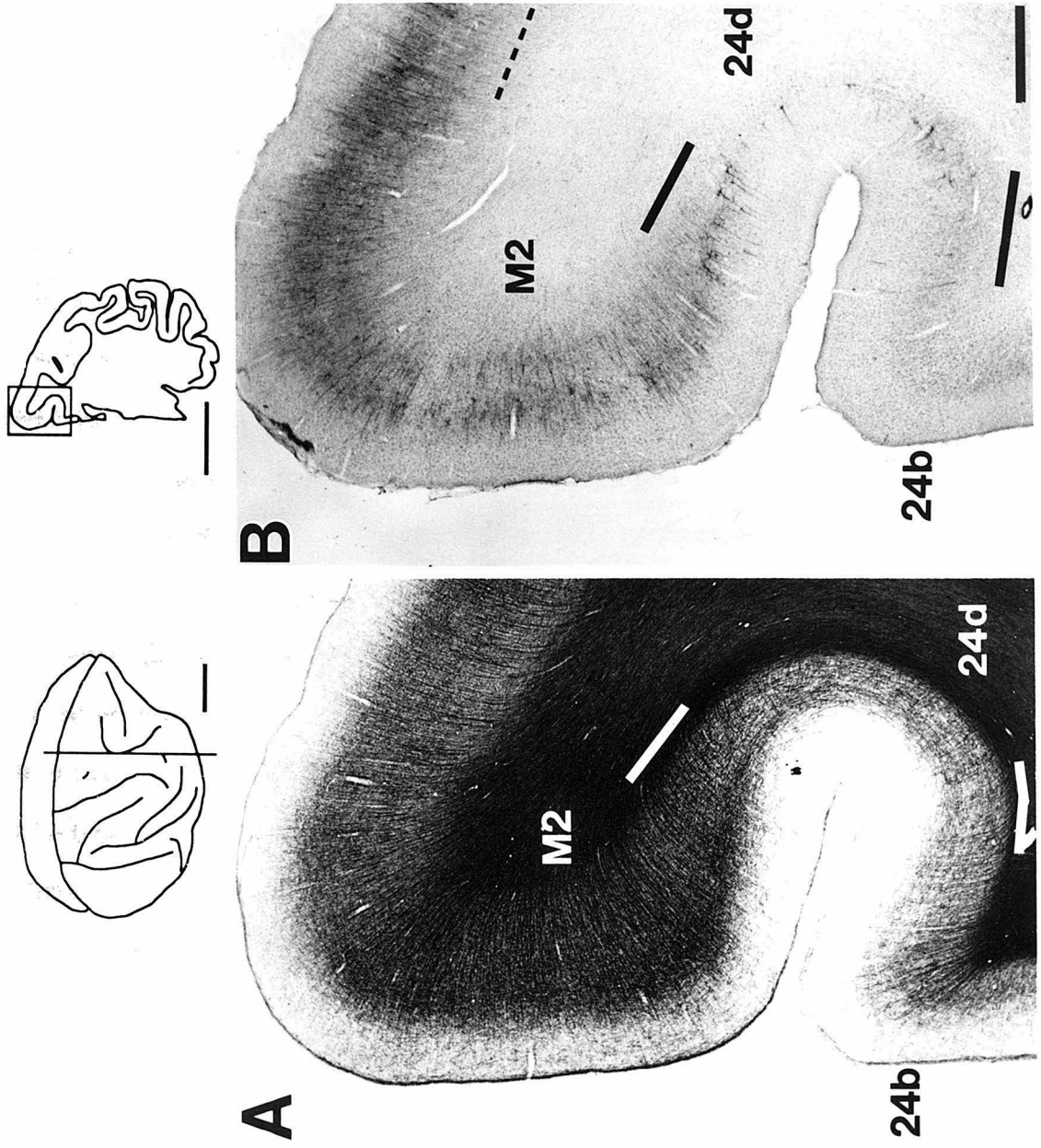


Figure 21. Coronal sections at the level of the posterior arcuate of case 95DR stained for myelination (**A**) and SMI-32-ir cell label (**B**), illustrating area 24d of the cingulate sulcus. The sections illustrated include a portion of M2 that projected to VIPm (Chapter 3). Panel scale is 1 mm, and inset scales are 1 cm.



contain a mixture of dense SMI-32-ir labeling (area 45 and 8Ac) and lighter SMI-32-ir labeling (6Vam and 8Am).

Cingulate cortex. In parceling cortex along the medial wall, we largely adopted the cytoarchitectonically derived cingulate subdivisions 23a, 23b, 23c, 29, 30, and 31 described by Vogt et al., (1987), and 24a, 24b, 24c and 24d by Matelli et al., (1991) (Fig. 13I). As shown in Figure 21, area 24d was further characterized by light myelination with a single band including layers 3 through 6, and a very light but consistent band of SMI-32-ir labeled cells in layer 3. The M2/24d border was characterized by considerably denser myelination in M2, which corresponds with denser SMI-32-ir cell and dendrite label in layers 3 and 5. The borders of M2, however were principally derived from cytoarchitectonic criteria (Barbas and Pandya, 1987). In lower portions of Figure 21, the zone 24b was characterized by moderately dense myelination and a prominent radial component, and by an absence of SMI-32-ir cell label. Other cingulate areas along the ventral medial wall were also nearly devoid of SMI-32-ir cell label, including 23a, 23b, and 24a.

Areal heterogeneity

Regarding modulations of staining within an area, Hof and Morrison (1995) have reported greater SMI-32 immunoreactivity for peripheral than for foveal representations of V1. In the many topographically organized visual areas examined in the present study, we found a suggestion of similar trends in V3, V4, MT, PO, and possibly VP and the MST complex. Likewise, in somatosensory areas 1, 2, and the S2 complex, regions corresponding to the

estimated face and possibly digit representations tended to be less heavily labeled with SMI-32-ir cells than portions representing the trunk and leg. However, given the vagaries of staining density across sections, such trends across sections can only be proven by rigorous quantification. Nonetheless, such trends at least serve as a reminder that there can be rational bases for gradients and trends of staining patterns within many of the areas and zones throughout the hemisphere.

Correlations across different stains

There were striking differences in the density and distribution of SMI-32 immunoreactive neurons and dendritic label predominantly throughout dorsal portions of the hemisphere, as has been described for visual-related cortex (Hof and Morrison, 1995), for areas in the superior temporal sulcus (Cusick et al., 1995; Hegdé and Felleman, 1995), and in the orbital and medial prefrontal cortex (Carmichael and Price, 1994). Moreover, in most dorsal regions of cortex, the density of SMI-32 immunoreactive cells in layers 3 and 5 correlated (at least qualitatively) with the relative density of myelination. This was particularly true of areas in and around the IPS, central sulcus, arcuate sulcus and portions of the lunate, parieto-occipital, lateral, and cingulate sulci. Areas where this correlation was most consistent included LIPv, VIPl, VIPm, portions of area 5, areas 1, 2, 4, 6DC, 4C, 6Val, V3, PO, PIP, A1, and Toc. Notable exceptions wherein areas contained overall dense myelination but relatively light SMI-32-ir cell label included portions of S2, 7a/7b, Tpt, V4, TEad/TEav, and ventral portions of the temporal lobe. However, no cortical regions were observed that contained densely populated SMI-32-ir cell label together with relatively light myelination.

The staining patterns of CAT-301 and SMI-32 were closely correlated in density and laminar distribution throughout most of the hemisphere. The SMI-32 antibody labeling was generally more robust, and easier to recognize as it predominantly labeled cells plus basal and apical dendrites (Campbell and Morrison, 1989; Hof and Morrison, 1995). CAT-301 histology, which labels the extracellular matrix as well as cell bodies (cf. McGuire et al., 1989; DeYoe et al., 1990), gave less consistent results overall and was therefore used to supplement the analysis of SMI-32-ir patterns. A positive correlation between CAT-301-ir label density and myelination density was observed, as has been previously reported (McGuire et al., 1989; DeYoe et al., 1990).

We examined the SMI-32-ir labeling for systematic correlations with sulcal and gyral geography. Cell label tended to be lighter along the fundi of most sulci relative to the neighboring sulcal banks, even when taking into consideration differences in cortical thickness. This was true for several areas occupying portions of different fundi, including areas of the IPS (PIP, VIPl, V3A, and possibly AIP), the STS (IPa, MSTm), the central sulcus (area 3a), the arcuate sulcus (8Am, 6Vam), and the lateral sulcus (Pi, and possibly Ri). Some notable exceptions included areas MT (which lies along a "soft" fundus), MSTa, gustatory cortex (G), and portions of the S2 complex (along the superior limiting sulcus). Surface cortex often showed lighter label than deep lying regions (buried in sulci) with the notable exceptions of areas 4, 1, 2, and portions of areas 5 and premotor cortex.

DISCUSSION

The purpose of this study was to better understand the layout of architectonically defined cortical areas and the degree of individual variability within the IPS and areas throughout the hemisphere to which this region is connected. We generated detailed cortical maps specific to each animal, containing architectonically defined landmarks that could be consistently identified across hemispheres (Figs. 12, 14, and 15). Within each intensively analyzed cortical hemisphere, excluding portions of the frontal lobe and temporal pole, we recognized over 70 architectonically distinct areas and zones.

In the course of analysis, we found many new zones that were distinctive, though it remains unresolved as to whether they represent distinct areas or subdivisions. Regardless of the semantics, charting the extent of architectonic areas and zones, their location relative to geography, and their degree of individual variability was invaluable for analysis of connectivity patterns (Chapter 3). With regard to brain mapping, these data are amenable to being directly incorporated in atlases of the macaque monkey, eventually they will aid in generating probability maps for the location of different cortical areas and landmarks relative to sulcal boundaries. These data should be useful for a variety of studies in the future, including physiological and connectivity studies, where it is not always feasible to identify architectonic parcellations in individual experimental hemispheres.

Comparisons to previous architectonic studies

Parietal/Intraparietal cortex. The architectonic distinctness of zones 7t, LOP and (albeit to a lesser extent) VIPm and VIPl, raises the question of whether they represent subdivisions or separate areas.

Zone 7t has been included as part of area 7 or 7b (Mountcastle et al., 1975; Jones and Burton, 1976; Leinonen and Nyman, 1979; Dong et al., 1994), as part of area 5 (Pons and Kaas, 1986), and as a separate region termed 2v based on cytoarchitecture and physiology (Schwarz and Fredrickson, 1971, 1974; Büttner and Büttner, 1978). Zone 7t overlaps cortex shown to receive concentrated inputs from vestibular nuclei (anterior area 7ip of Akbarian et al., 1994), and may also contain single cell vestibular response properties (area 2v of Büttner and Büttner, 1978; but also see Grüsser et al., 1990). Additionally, cortex in the vicinity 7t is thought to include a separate and rather extensive mouth or face representation based on physiological recording from the tip region of the IPS (Leinonen and Nyman, 1979).

The zone LOP was previously included as part of V3A (Gattass et al., 1988), PIP (Colby et al., 1988; Felleman and Van Essen, 1991; Felleman et al., 1997). Additionally, portions of LOP may also have been included as part of LIPv, and based on geography, and may be connected with the frontal eye fields (Schall et al., 1995: Figs. 9-13). LOP also appears to be connected with PO (Colby et al., 1988) and V3 (Felleman et al., 1997).

Area VIP has formerly been regarded as a single area both on physiological grounds (Colby et al., 1993) and in part on architecture (it is part of area IPd of Seltzer and Pandya, 1986). Physiologically defined VIP, which is based primarily on the presence of cells with a high degree of selectivity for the direction of a moving stimulus, extends 2 to 5 mm up both the medial and

lateral banks of the IPS (from the white matter boundary at the fundus), along the middle third of the IPS (cf. Colby et al., 1993: Fig. 1). This location is consistent with our findings, though the medial border (VIPm/5V) was more variable in this study. In some cases, the core region of VIPm appears to have extended further dorsal along the medial bank of the IPS than was suggested by the above authors, which may be due to differences in the species used (*M. fascicularis* versus *M. mulatta*).

The VIPm/VIPl transition region was often located close to the base of the fundus, and thus unlikely to correspond to the medial border of physiologically defined VIP. Additionally the location of the VIPm/5V border was supported by connectivity patterns with different visual- and sensorimotor-related areas, while connection differences between VIPm and VIPl were related more to the relative strengths of inputs rather than different areas (Chapter 3).

The anterior and posterior boundaries of VIP were more subtle in coronal sections, resulting in relatively large transition regions in our maps. The location of the VIP/PIP and VIP/AIP boundaries were consistent with the location of the MT projection zone that originally defined this area (Van Essen et al., 1980; Ungerleider and Desimone et al., 1986b; also see Chapter 3). Determining the antero-posterior extent of VIP is of particular interest, as the transitional region may contain a head as well as hand/arm representation (see Chapter 3).

Of the seventeen architectonic areas and zones we identify in the IPS/POS region, 14 have been previously described, though not all of these 14 have been mapped completely in individual hemispheres. This is in part due to difficulty with delineating subtle architectonic boundaries, and in part with the effort involved in representing all the architectonic data. Of the areas we

identified, there is general agreement of the architectonic identity of LIPv (Blatt et al., 1990; also VIP*, Ungerleider and Desimone, 1986; also POai, Seltzer and Pandya, 1980), LIPd (Blatt et al., 1990; also POae, Seltzer and Pandya, 1980), the 7a/7b complex (Pandya and Seltzer, 1982; Preuss and Goldman-Rakic, 1991b), V3 (also V3d, Burkhalter et al., 1986; Gattass et al., 1988; Felleman et al., 1997), PO (also V6) (Colby et al., 1988; Galletti et al., 1996), and area 5 (Jones et al., 1978; Pons et al., 1985; also area PE subdivisions Pandya and Seltzer, 1982). Other areas have been mapped with more variability, including areas AIP (Preuss and Goldman-Rakic, 1991b), MIP, V3A, and PIP (Colby et al., 1988; Gattass et al., 1988). The newly identified zones 7t, LOP, VIPm, and VIPl, were generally comparable in robustness as many of the above mentioned areas, and were consistently identifiable in nearly all hemispheres studied.

Areas of the STS. Our analysis of the STS includes newly identified zones MSTdp and ITd. The architecture of MSTdp was more similar to MT than surrounding portions of MST, but the MST root was retained in part because of its connections, which include projections from MT, but not from V1 (Chapter 3). The location of MSTdp may correspond to a V2 recipient region lying outside of MT* described by Ungerleider and Desimone (1986a), and appears to lie dorsal to their subdivision MTp, which they describe as receiving V1 and V2 inputs. MSTdp may have been included as part of area MT in other studies due to similarities in SMI-32 cell label and myelination (Hof and Morrison, 1995; Cusick et al., 1995). Outside of the combined MT/MSTdp region, the other salient areas/zones of the posterior STS included FST and MSTda (densely myelinated zone) of Desimone and Ungerleider (1986), and the lateral borders TPOc and TPOi (Cusick et al., 1995). The correlation between the MSTm and

MSTdp subdivisions with other studies (physiological) remains to be determined.

Zone ITd was identified along the ventral bank of mid-portions of the STS, based primarily on the presence of relatively dense SMI-32 immunoreactivity. However, other studies have more finely parceled this region based on cytoarchitecture and myeloarchitecture (Seltzer and Pandya, 1978; Preuss and Goldman-Rakic, 1991b), including boundaries that were evident in several sections of our tissue, though less robust than the SMI-32-ir pattern of label. Thus, ITd may contain two subdivisions or areas extending along the antero-posterior axis, including TEa and part of TEm (ibid.). Alternatively, connections with this region would suggest three separate areas splitting ITd about the shorter medio-lateral axis, including areas PITd, CITd, and AITd. Modulations in SMI-32 immunoreactivity may also support these subdivisions, based on the density, which decreases in anterior portions of the STS.

Frontal cortex. Our results from SMI-32 immunoreactive staining in frontal cortex showed additional support for the distinction of area 24d of Matelli et al., (1991) and at least the lateral border of M2 of Barbas and Pandya (1987). M2 appears to overlap the face and arm representation of F3 of Luppino et al., (1993), and M2 together with medial portions of 6DC may overlap area 6M of Preuss and Goldman-Rakic (1991a), all of which appear to overlap the classically defined supplementary motor area (Woolsey et al., 1952).

Global parcellations and flat maps

One goal of architectonic analysis is to identify a unified set of cortical areas for the entire cortical hemisphere of the macaque monkey, with the assumption that there is sufficient consistency for a canonical brain map to be demonstrated. Another goal is to chart the nature and extent of individual variability. In this study, we primarily selected previously defined criteria for identifying cortical areas throughout the hemisphere, with the intent on representing areas that appear robust across multiple studies. Additionally, we incorporated the use of core outlines (excluding transition regions and regions of uncertainty) and different thicknesses of outlines to represent cortical landmarks, resulting in relatively conservative architectonic maps. However, many areas are controversial and the parcellation maps in this and other studies will presumably be subject to continued refinement and revision.

Toward generating an architectonic map atlas, several issues and obstacles must be overcome, including addressing inherent differences across architectonic studies, and a means of carefully comparing results across studies. With regard to the former problem, different studies have used different protocols and combinations of histological stains to parcel cortex, thereby yielding different maps. Additionally, the interpretation of architectonic differences and the placement of cortical boundaries has often been subjective, in that different aspects of staining patterns may have been arbitrarily chosen over others for parceling. Another caveat is that different species of the macaque have been used for identifying cortical areas, which may account for differences in the locations of some borders and possibly the architectonic identity of numerous regions. Thus, multiple schemes may need to be represented or incorporated when generating probability maps.

With regard to comparisons across studies, multiple formats for data illustration will continue to be important, one of which includes cortical flat maps. Flat maps allow all of cortex to be viewed in a single map (including architectonic borders, connectivity data, functional data, etc.). They are also well suited for surface-based warping into other maps, which allows one map (even partial maps) to be deformed to match the shape of another (Drury et al., 1996b, 1997). This method, as distinct from simply scaling, aligning, and superimposing maps from different hemispheres on to one another, allows for more accurate alignment of global as well as local cortical features. Additionally, map warping can be driven by a variety of different brain mapping features, including geographical landmarks, architectonic landmarks, or a combination of both. This approach has much potential for generating architectonic maps that reflect individual variability and thus the probability that a given geographic location belongs to one or another subdivision, a feature that should prove useful for a wide variety of brain mapping studies. Portions of these data are available at our WWW site (<http://v1.wustl.edu>).

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APPENDIX A: Architectonic Parcellation of Cerebral Cortex in the Macaque Monkey

In parceling the cortex of the macaque monkey, we have adopted architectonic definitions from several studies described in the text and below. The core extent of architectonically identifiable areas and zones were delineated primarily by the combined analysis of myeloarchitecture, cytoarchitecture, and SMI-32 immunoreactivity patterns, and by referring to the results of previous mapping studies. Additionally, CAT-301 immunoreactivity patterns and acetylcholinesterase staining were also analyzed in some cases.

We describe the characteristic staining patterns of over 65 areas and zones delineated in this study. The trends in differential staining patterns at subtle borders are also addressed, as relative differences were often more useful for delineating boundaries than absolute patterns due to the variability across cases (i.e., genuine individual variability, tissue quality, morphology-related artifacts, etc.). Descriptions of posterior regions of the hemisphere (posterior to the central sulcus) are based on the analysis of 14 hemispheres from 10 animals. The analysis of architectonics in the anterior portions were derived from 5 hemispheres from 5 animals.

Descriptions of cortical areas are organized roughly from posterior to anterior and under five main headings: visual, somatosensory, cingulate, motor and premotor, prefrontal, and auditory-related cortex. Within these headings, cortical areas are organized in order of hierarchy, if known (cf. Van Essen, et al., 1990). To avoid redundancies in descriptions of subtle areal transitions, the posterior-most borders of an area are generally described in its given caption.

Visual cortex

V2. Two myeloarchitectonic patterns were observed in V2 (Colby et al., 1988), including a thick single dense band covering layer 4 to layer 6, with weak staining in upper layers, and in other regions a clear bilaminar appearance with a stronger radial fiber component. In SMI-32 stained sections, V2 had a moderately dense band of small- and medium-sized labeled cells in layer 3, and sparse to moderate cell label in layer 5, in agreement with Hof and Morrison (1995). The CAT-301 antibody stains were similar to those of SMI-32 (DeYoe et al., 1990). Furthermore, modulations of both CAT-301 and SMI-32 immunoreactivity was evident in the supragranular layers of some cases, with roughly the same spatial frequency as reported with the cytochrome oxidase thick and thin stripes of V2 (cf. DeYoe et al., 1990).

Area V2 borders with V1, V3, VP, PO, and sometimes TF. The transition from V2 to VP (not outlined in this study) was not well defined architectonically, though there was a general trend of decreasing density of SMI-32 label in cortex extending anterior of V2. Also, in myelin stains, the two bands of Baillarger tend to fuse in further anterior sections, giving the appearance of a single band that spanned layer 2/3 to layer 6.

V3. Area V3 (also V3d) is located along the annectant gyrus, and along the fundus of the lunate further lateral. In some cases, V3 was divided into two regions, due to difficulty in delineating a continuous outline with coronal sections. Along the annectant gyrus, V3 stands out as a densely myelinated region (Burkhalter et al., 1986), with denser label in deep layers that sometimes appears as a single dense band (layers 3 through 6) having a matted

appearance (Van Essen et al., 1986). In some cases the bands of Baillarger had a more bilaminar appearance, in which case transitions were determined by the overall density and other stains. Along the fundus of the lunate, V3 also had a matted appearance, though the density was lighter than in more medial portions of V3 (peripheral representation). Additionally, the inner band of V3 was often not well separated from white matter (Colby et al., 1988), distinguishing it from V2 in some sections.

SMI-32-ir label in V3 was distinctive, having a densely packed band of cells of medium size in layers 2 and 3, plus a band of medium to large pyramidal cells in layer 5 of lower density (Hof and Morrison, 1995). CAT-301 labeling in V3 was characterized by bands of label in layers 5a and 6, giving it an overall trilaminar appearance (DeYoe et al., 1990). Both antibody stains showed lighter label in V3 along the lunate fundus than on the annectant gyrus. V3 shares borders with V2, V4, V3A, PIP, and sometimes PO.

VP. Area VP (also V3v) was not explicitly identified architectonically in this study. However, the estimated region of VP (Burkhalter et al., 1986) was in part characterized in myelination by a single, moderately dense band that spanned layers 3 through 6. The overall density was comparable to V2 and V4 , consistent with.

V3A. Area V3A covered the floor of the lunate sulcus anterior to the annectant gyrus (Van Essen and Zeki, 1978; Gattass et al., 1985, 1988), and was characterized by relatively light myelination, with two thin bands having prominent tangential fibers in most portions of this area. The bands were well separated from each other in most sections (Colby et al., 1988). V3A was also characterized by SMI-32-ir label with a thin band of deep layer 3 label and few

layer 5 cells. This description differed from that by Hof and Morrison (1995; Fig. 1). Physiologically defined V3A was likely to extend beyond the core region we identified architectonically.

V3A borders V3, V4, DP, PIP, and LOP. Area V3 was much denser overall in myelination than V3A, and V3 did not contain the distinctive tangential fibers of V3A. Similarly, in SMI-32 sections, V3 was denser overall, especially in layer 3, whereas V3A shows a distinctively thin and well organized band of SMI-32-ir cells in layer 3.

LOP. Zone LOP (lateral occipital parietal) is located on the dorsolateral bank of the IPS/lunate confluence, dorsal and anterior to the annectant gyrus. LOP was more densely myelinated than surrounding cortex, and had a slight to moderate degree of banding with a matted appearance. In many cases, an denser outer band of myelination distinguished LOP from V3A, and the band was usually well separated from an inner band. LOP also had considerably denser SMI-32-ir cell label than surrounding cortex, showing a densely packed band of cells in layer 3 with medium size neurons, plus a band of medium sized layer 5 neurons. LOP borders V3A, LIPv, DP, and sometimes PIP and VIPl.

PIP. Area PIP lies along the posterior fundus of the IPS where it joins the parieto-occipital sulcus. In myelin stains, PIP was lighter than adjacent areas PO and V3 (Colby et al., 1988). Two bands were evident in some sections, with tangential fibers along the fundus, though appear to fuse in others. In SMI-32 sections, PIP had a light to moderately dense layer 3 band of cells and a lighter band in layer 5.

PIP shares borders with areas V2, V3, PO, VIP1, and less distinctly with areas V3A, LOP, and MIP. The transitions along the antero-posterior axis were subtle, often resulting in highly truncated core outlines. The PIP/V2 transition was distinguished by the broader and denser band of SMI-32-ir cells in layer 3 of area V2.

PO. Area PO lies along the anterior bank of the parieto-occipital sulcus, extending along both the medial wall and into the medial bank of the IPS (Colby et al., 1988). In myelin, PO was relatively dense, had clear inner and outer bands of Baillarger, and often a strong radial component (Colby et al., 1988). The SMI-32 staining pattern showed distinctively broad and dense band in layer 3 with medium sized cells, plus a lighter band of cells and fibers in layer 5 and sometimes layer 6 (Hof and Morrison, 1995). In CAT-301, staining in layer 3 was denser than surrounding cortex. In Nissl stains, PO often contained a relatively high density of medium sized layer 3 cells with a well organized columnar appearance. PO shares borders with V2, MDP, MIP, and PIP. The V2/PO border was most readily distinguished in SMI-32-ir stains, in which the layer 3 band of cells in PO is denser and sometimes considerably broader.

V4/DP/VOT. Areas V4, DP, and VOT were outlined together, due to subtleties in defining their common boundaries, and modularity within V4. Area V4 was characterized primarily by myelination, having relatively thin and distinct inner and outer bands of Baillarger that were well separated from each other and from the white matter (cf. Colby et al., 1988). The outline of V4/VOT were also based in part on geography, in accord with physiological studies (Gattass et al., 1988). In sections stained with SMI-32, the gyral portion of V4 had a

very thin layer 3 band and sparsely distributed medium-sized pyramidal cells in layer 5, which correlated well with the V4/V4t myelin border. The density of SMI-32-ir label increased along the anterior bank of the lunate, as well as in other regions, showing a modular organization along the dorso-ventral axis, and thus unlikely to correspond to neighboring areas VOT or VP. Dorso-medial portions of V4 contained SMI-32-ir cell label that differed from that shown by Hof and Morrison (1995), and possibly Cusick et al., (1995). Other borders of V4 include V2, V3, VP, V3A, DP, V4tp, V4ta and ITd.

Ventral portions of V4 were difficult to distinguish from VP, and were labeled to reflect the degree of ambiguity on the flat maps. The dorsal prelunate area (DP) was defined in cytoarchitecture by a relatively dense layer 4, and poorly differentiated layers 5 and 6, and thinner but denser bands of Baillarger than 7a (May and Andersen, 1986; Andersen et al., 1990). In myelin, DP shows a staining density similar to V4 and LIPd, though often not having as clearly separated bands of Baillarger. In SMI-32 sections, DP shows a light to moderate band of label in layer 3 (Hof and Morrison, 1995), which was greater than in dorsal portions of V4. Relative to V3A, the band of SMI-32-ir label in DP was generally thicker than and less organized in appearance. Overall, zone LOP was denser SMI-32-ir cell label and myelination than DP. DP borders areas V4, V3A, LOP, 7a, LIPd, and sometimes LIPv.

V4t subdivisions. Area V4t was subdivided into a posterior and anterior portion. The posterior division, V4tp, lies between V4, MT, and V4ta, along the posterior bank of the STS. V4tp corresponds most closely with the architectonic description of V4t in other studies, being intermediate between V4 and MT both in myelination (Desimone and Ungerleider, 1986) and SMI-32-ir cell label (Cusick et al., 1995). V4tp had poorly developed bands of

Baillarger, with often a broader and denser inner band. Area V4 was distinguished from V4tp by lighter overall SMI-32 label, and a thinner band of labeled cells in layer 3. In myelin, V4 was less dense than V4tp overall, had a more prominent outer band, and often has a stronger radial component.

The anterior division, V4ta, was distinguished from V4tp by its more prominent, dense band of SMI-32-ir layer 3 pyramidal cells, in addition to heavier myelination with a stronger radial component. The architecture of V4ta in our tissue appeared as transitional between V4t proper and ITd, though overlapped physiologically defined portions of V4t, and thus the root name was preserved (Desimone and Ungerleider, 1986). V4ta borders V4, V4tp, MT, and ITd.

MT. MT was characterized by a single, dense band of heavy myelination that is matted in appearance, and occupies all of layers 4 and 5 and often layer 6 (Van Essen et al., 1980; Desimone and Ungerleider, 1986). MT showed a trilaminar pattern of densely stained SMI-32-ir cells and dendrites, similar to descriptions by Cusick et al., (1995) and Hof and Morrison, (1995). Additionally, dorsal and posterior portions of MT were overall denser than anterior portions, though both retained a trilaminar organization. Dense SMI-32-ir label in layer 3, large pyramidal cells in layer 5, and medium sized cells in layer 6 were often distinguishing from surrounding cortex. In CAT-301 sections, label in MT was very dense overall, standing out from V4tp (DeYoe et al., 1990). Area MT shares borders with V4tp, V4ta, FST, MSTdp, and less distinctly with 7a, V4/DP, and ITd. The lightly myelinated subdivision MTp of Desimone and Ungerleider (1986), was not explicitly represented in our maps, though is likely to be located in the MT/MSTm/MSTdp transition region.

MST subdivisions. The MST complex was subdivided into dorso-posterior (MSTdp), medial (MSTm) and dorso-anterior (MSTda) regions. The dorso-posterior subdivision, MSTdp, was characterized by heavy myelination and SMI-32-ir and CAT-301-ir label, similar to the label observed in MT. The principal architectonic difference from MT was that MSTdp contains a more banded appearance in myelination, and often a slight radial component than MT. In SMI-32 sections, the MT/MSTdp transition was often subtle, but with MT being characterized by stronger label in layer 6, and an overall denser and more organized laminar appearance. MSTdp borders MSTm, MT, and less sharply with 7a and possibly V4. The V4/DP transition to MSTdp was gradual, and often compromised by the coronal plane of sectioning, resulting in a large uncertainty region.

The medial subdivision, MSTm, occupies much of the medial fundus of the posterior STS, and was characterized by relatively light myelination, including a single band spanning layers 3 through 6. This region was also characterized by moderate to light SMI-32-ir cell label in layer 3 throughout the core extent. MSTm borders 7a, MSTdp, MSTda, and sometimes FST.

The dorso-anterior subdivision, MSTda, corresponded to the densely myelinated zone (DMZ) of Desimone and Ungerleider (1986), occupying the dorsal bank of the STS near the medial fundus. The border with TPOc was subtle in some sections, but distinguished by the denser myelination of MSTda, and more continuous SMI-32-ir cell label in some cases (Cusick et al., 1995). MSTda borders MSTm, TPOc, and sometimes TPOi.

FST. Area FST lies along the broad, flat fundus of the STS, and was characterized by dense radial bundles extending from the white matter to supergranular layers (Desimone and Ungerleider, 1986). The posterior border

of FST wedges in between MT and MSTa, and had distinctive borders, as neither MT nor MSTa show prominent radial bundles. In SMI-32 sections, layer 3 of FST showed a thin to moderately broad band of medium to small sized pyramidal cells that were loosely packed, and fewer cells in layer 5. The layer 3 band of labeled cells was narrower and less dense than in neighboring MSTa and ITd, and corresponds with the myelin transitions well. FST borders MT, MSTm, TPOi and TPOr, ITd, and IPa.

MIP. Area MIP lies in the posterior portion of the IPS on the medial wall, extending from dorso-posterior to ventro-anterior portions. MIP was primarily delineate in myelin stains by a thin dense inner band of Baillarger with relatively few vertical fibers that are separated from the white matter (Colby et al., 1988). The myelination was often less dense than surrounding areas 5 and PO. In SMI-32 stained sections, MIP had a relatively thin to moderate band of layer 3 pyramidal cells, and a sparser layer 5 (Hof and Morrison, 1995). The two bands of SMI-32 label were not as distinct or well separated as in PO (ventral) and anterior portions of area 5 (dorsal). In Nissl stains, MIP contained less intensely stained and smaller cells in layers 3 and 5 than area 5 (5D) dorsal to it. Also, layers 2 and 3 together were considerably broader than 5 and 6, as compared with dorsal and ventral regions. MIP borders PO, MDP, VIPm, area 5 (5V and 5D), and sometimes PIP and VIPl.

LIPd. LIPd lies within the upper lateral bank of the IPS, and characterized by relatively light myelination, and had a distinct bilaminar appearance (Blatt et al., 1990). LIPd was distinctively less dense overall than LIPv, and did not contain the thick radial bundles of 7a. LIPd showed a thin to moderate band of SMI-32-ir cell label in layer 3, and lighter distribution of medium sized cells in

layer 5. In some sections, the LIPd/LIPv border was striking in overall SMI-32-ir cell label density. In CAT-301 sections, two bands of label are evident in LIPd, which are intermediate in strength between LIPv and 7a, in agreement with McGuire et al., (1989). LIPd appears to coincide with cytoarchitectonically defined POa-e (Seltzer and Pandya, 1980). LIPd borders areas 7a, LIPv, AIP, and DP. The boundary between LIPd and DP was difficult to assess, being based both on a stronger radial component in DP, and on cortical geography (May and Andersen, 1986).

LIPv. LIPv lies along ventral portions of the lateral bank of the IPS, and was characterized by a prominent bulge of increased myelin density and a slight banded appearance (Blatt et al., 1990). This region was equally if not more evident in SMI-32 stains, in which LIPv contains a densely packed layer 3 and large and sometime conspicuous layer 5 pyramidal cells. CAT-301-ir labeling was similar to that of SMI-32-ir, where two bands of dense label are evident, though the transitions were less sharp (DeYoe et al., 1990: Fig. 1). The anterior border of LIPv with AIP was variable, due to a gradual decrease in myelination and size of the prominent cortical bulge. Some cases were suggestive of anterior subdivision of LIPv, being intermediate in myelination density between AIP and posterior portions of LIPv. LIPv overlaps with the cytoarchitectonic boundaries of POa-i (Seltzer and Pandya, 1980).

LIPv borders areas LIPd, VIPl, AIP, LOP, and possibly PIP. Relative to LOP, LIPv showed a stronger radial component and generally had more clearly separated bands of Baillarger. In most cases, a region of light SMI-32-ir label was present between LIPv and LOP, facilitating the distinction. Additionally, LIPv often contained large and conspicuous layer 5 pyramidal cells, which were not observed LOP.

VIPl. Zone VIPl (lateral division) lies along the fundus and lateral bank of the IPS at approximately the middle third of the sulcus. VIPl was always lighter in myelination and SMI-32-ir cell label than neighboring area LIPv, and was typically lighter than VIPm. In myelin stains, VIPl was characterized by a single light band of myelinated fibers (layers 3-6). In SMI-32 sections, VIPl was characterized by medium to small sized deep layer 3 pyramidal cells with light to moderate overall density, and by a much sparser distribution of medium to large layer 5 pyramidal cells with long basal and apical dendritic processes. Nissl stains were not used to differentiate the boundaries of VIPl. However, Seltzer and Pandya, (1986) have identified a region termed IPd that overlaps VIPl and possibly portions of VIPm, AIP and the PIP/VIPl transition region of this study. VIPl borders LIPv, VIPm, AIP, PIP, and sometimes MIP. The transition from VIPl to PIP was subtle, with PIP being characterized by a thicker band of SMI-32-ir labeled cells in layer 3, and in some cases a more banded appearance in myelination.

VIPm. Zone VIPm (medial division) lies along the fundus and medial bank of the IPS. In myelin, VIPm appeared as a single, thick band occupying layers 3 through 6, and had a matted appearance. The VIPm border with 5V was best characterized in myelin stains, in which 5V showed two clear bands of Baillarger. In posterior portions of 5V, the myelination was lighter overall than VIPm, while in anterior portions 5V was typically denser. In SMI-32 sections, VIPm was often characterized by a relatively broad and dense band of label in layer 3, and a sparser distribution of pyramidal cells in layer 5. In some sections, this pattern of label appeared nearly continuous with 5V, and was not always reliable for discerning its dorsal boundary with 5V. The

VIPl/VIPm boundary was subtle in some cases, being characterized by a gradient, and rarely a sharp transition. In cases and sections where two subdivisions were not evident, myelination and SMI-32-ir cell label was generally lighter than surrounding cortex, similar to the description for VIPl. The cytoarchitectonic border PEa/IPd described by Seltzer and Pandya (1986) was evident in many sections, and correlated with the 5V/VIPm transition in myelination.

VIPm borders 5V, MIP, VIPl and AIP. The MIP/VIPm transition was best defined in myeloarchitecture, in which the thin, dense inner band of Baillarger defining MIP merges with the outer band of Baillarger, appearing as a thicker, single band spanning layers 3-6, characteristic of VIPm. In SMI-32 sections, this transition was more subtle, often being characterized by denser label in VIPm, and a less organized laminar appearance.

MDP. The medial dorsal parietal area, MDP, is located on the medial wall posterior to the cingulate sulcus extending to the parieto-occipital sulcus (Colby et al., 1988), and was best characterized by myelination, having two well separated and dense bands of Baillarger, and a strong radial component. In SMI-32 stained sections, MDP contained a lightly distributed small to medium-large sized pyramidal cell bodies in layer 3 and to a lesser extent layer 5. In some sections, cells had thick and conspicuous apical dendrites, further distinguishing this area from surrounding cortex. MDP overlaps area 7m (Stanton et al., 1977; Preuss and Goldman-Rakic, 1991b), but did not extend as far ventral as 7m. MDP may overlap area PGm of Pandya and Seltzer (1982).

MDP borders area PO, 31, 5D, and less distinctly with MIP and cortex further ventral. MDP was more heavily myelinated than 5D, and had coarser radial fibers than area PO, and lighter overall. SMI-32-ir label in layer 3 was

stronger and more continuous in appearance in MDP than cortex ventral and dorsal to it, but less dense overall than area PO (in posterior portions). The transition to area 31 was subtle, with 31 being characterized by lighter myelination and SMI-32-ir label. In Nissl stains, 5D showed medium to large layer 3 and layer 5 cells that were absent in MDP.

7a and 7b. Areas 7a and 7b were outlined together as one region. Both areas were principally defined by myeloarchitecture, but also by SMI-32 antibody staining patterns. Area 7a (also PG) was located along medial portions of the intraparietal lobule. In myelin, 7a was heterogeneous, having a strong radial component, especially at the ridge of the IPS and extending to the ridge and sometimes dorsal bank of the lateral sulcus (7a-m and 7a-l of Preuss and Goldman-Rakic, 1991b; also see Andersen et al., 1990). In SMI-32 antibody stained sections, 7a was distinguished from surrounding cortex by its relative lack of label, containing few sparsely populated and weakly labeled cells in layer 3 and sometimes layer 5. This observation is different from the label observed by Hof and Morrison, (1995), who found prominent bands of cell label in layers 3 and 5. Area 7a bordered areas LIPd, DP, MST, 7b, TPOc, and sometimes V4 and 7op. The 7a/DP border was distinguished by the presence of light to moderate SMI-32-ir label in DP. The 7a/MSTm border was characterized by a strong increase in SMI-32-ir cell label. Area 7a contained sparser SMI-32-ir cell label than LIPd, and also a much stronger radial component in myelination.

Area 7b (also PF) lies lateral and anterior to 7a, and showed a gradual increase in density versus 7a, including thick vertical fibers, a prominent and broad outer band and a lighter inner band (Preuss and Goldman-Rakic, 1991b). In 7b, SMI-32-ir cell label was light, but more numerous than in 7a (gradual

transition), and were of small to medium size along a relatively thin band in layer 3. In Nissl stains, much of 7b was characterized by a columnar appearance (Preuss and Goldman-Rakic, 1991b), though this feature was subtle for delineating borders. Area 7b bordered areas 7a, 7op, 7t, 2, and sometimes AIP and LIPd.

IPa. IPa is located anterior to FST along the flat fundus of the STS, including portions of both the superior and inferior fundi (Cusick et al., 1995). IPa was lightly myelinated overall, having a distinct, thin outer band of Baillarger, plus lighter myelination in lower layers that merged with the white matter. In SMI-32 sections, IPa was more lightly populated than neighboring areas TPOr and ITd, having small to medium cells in layer 3, and to a lesser extent in layers 5 and 6. Area IPa overlaps areas IPa and PGa of Seltzer and Pandya (1978), and Preuss and Goldman-Rakic, (1991b).

IPa borders areas TPOr, ITd, FST, and cortex further anterior along the fundus of the STS. The anterior border with IPa, where the two fundi of the STS merge into one, had similar architectonic features to IPa, but was more subtle due to the tight folds. This regions was more lightly myelinated overall, has less well separated bands of Baillarger, but did not as clearly show radial bundles. SMI-32-ir label was similar in both regions, though lighter further anterior.

TPOc. Area TPOc is located along the posterior portion of the dorsal bank of the STS, and was defined by myelination and SMI-32-ir label (Cusick et al., 1995). TPOc was characterized by moderately dense myelination and poorly separated bands of Baillarger, lacking the radial component of cortex further dorsal (7a) and lacking the density of cortex further ventral (MSTda). In SMI-

32 sections, TPOc was characterized by a dense layer 3 band of label with medium to large pyramidal cells, and a thinner band of label in layer 5 with large and some medium cells. In some sections, clusters of SMI-32-ir cells in layers 3 and 4 were observed, consistent with the above authors. Nissl stained sections showed a distinctive layer 3 and layer 5 band of medium sized cells. TPOc borders areas 7a/7b, MSTda, Tpt, TPOi, and less distinctly with Toc. In some cases, the TPOc/MSTda border was quite subtle, and together TPOc and MSTda appeared as one architectonic zone with dense myelination, SMI-32-ir and CAT-301-ir cell label.

TPOi. Area TPOi is the anterior continuation of TPOc along the dorsal bank of the STS (Cusick et al., 1995). TPOi had moderately dense myelination and two distinct bands of Baillarger, though slightly lighter than that of TPOc. Additionally, SMI-32-ir cell density was less than in TPOc, and more evenly distributed, though the border can be subtle in the coronal plane. Other borders of TPOi include Tpt, MSTda, TPOr, and sometimes FST.

TPOr. TPOr is anterior to TPOi along the STS dorsal bank, and generally occupying an accessory gyrus (Cusick et al., 1995). In myelin, TPOr was moderately stained, has two well separated bands of Baillarger (broader than TPOi), and fine radial fibers. In SMI-32 sections, TPOr has moderately dense cell label and a broad layer 4, distinguishing it from neighboring areas TAa and IPa (also see Seltzer and Pandya, 1978). TPOr borders TPOi, TAa, IPa, FST, and sometimes Tpt.

ITd. The dorsal inferotemporal area, ITd, occupies the ventral bank of the STS along the middle third of the sulcus. The most prominent characteristic is the

relatively strong SMI-32-ir label in layer 3 (Hegd  and Felleman, 1995), readily distinguishing it from TEad and IPa. In some cases, a lighter band of SMI-32-ir cells is also evident in layer 5 and in layer 6. In myelin, the two bands of Baillarger were well separated, moderately dense, and had a strong radial component. ITd overlaps areas CITd and portions of PITd and AITd, based on geography (Van Essen et al., 1990). ITd also overlaps portions of TEO (von Bonin and Bailey, 1947), and also portions of TEa and OAa (Seltzer and Pandya, 1978).

ITd borders areas V4ta, V4, IPa, and less distinctly with MT, FST, and TEad. The ITd/V4ta border was characterized by denser SMI-32 label in V4ta, and less prominent bands of Baillarger which was often a subtle border. ITd was much more densely populated with SMI-32-ir cells than V4. The ventro-lateral border of ITd merged into an uncertainty region in this study, containing portions of cyto- and myeloarchitectonically defined area TEm (Preuss and Goldman-Rakic, 1991b). TEm was not outlined in this study as the borders were more subtle in our tissue than ITd, and omitted for clarity. Further ventral to ITd (and TEm) is the dorsal border of area TEad (Saleem and Tanaka, 1996), which was distinguished based on cyto- and myeloarchitecture.

TF and TH. Areas TH and TF were included in a single outline, with TF defined in cytoarchitecture by a densely packed layer 6, and TH with a less distinct layers 5 and 6, and a granular layer 4 (von Bonin and Bailey, 1947; Seltzer and Pandya, 1976). TH had a distinct granular layer 4 while TF does not. In myelin, TF and TH were characterized by a single, light band including layers 3 through 6. In some cases, a thin, outer band of Baillarger was prominent throughout TF. Area TF/TH borders areas 36, TEav, the subiculum, and less distinctly with areas V2, VP, V4, and VOT (cf. Felleman and Van Essen, 1990). The cortex

posterior to TF was characterized in cytoarchitecture by a thinner and less prominent layer 6. Additionally, TF was more lightly myelinated than cortex further posterior.

TEad and TEav. Areas TEad and TEav were outlined together, and extend from the ventral shoulder of the STS to cortex medial to the anterior middle temporal sulcus (Saleem and Tanaka, 1996). In Nissl, TEad had a less prominent layer 3 than TEm (Preuss and Goldman-Rakic, 1991b). In myelin sections, TEad was characterized by relatively dense overall staining, and two well developed bands of Baillarger and a moderate radial component. TEav was more lightly myelinated and the bands are not as pronounced as in TEad. Both regions were largely devoid of SMI-32-ir cell label.

TEad and TEav together border ITd (and TEm), 36, the VOT/V4 region, and cortex further anterior (not included in this study). The TEav/36 boundary was distinguished in Nissl, where TEav had a more evident sublamination in infragranular layers, and larger layer 5a cells. In myelin, TEav showed two separated and prominent bands of Baillarger, which gradually merge into one very broad band in 36. The V4/VOT boundary with TEad and TEav was subtle, distinguished by the presence of a more prominent inner band relative to the outer band in VOT/V4, while TEad showed two equally dense and distinct bands. Also, the overall density of myelination was often greater in TEad.

36 and 35. Perirhinal areas 36 and 35 were often outlined together, and primarily defined by cytoarchitecture, where layers 5 and 6 appear to be merged, containing medium sized cells (Amaral et al., 1987; Saleem and Tanaka, 1996). Areas 36 and 35 were lightly myelination, with often a single band extending from layers 3 to 6. Area 35 border ER, and 36 borders TEav and TF.

The TF/36 boundary was evident in cytoarchitecture by the merging of medium sized cells in layers 5 and 6 of area 36, while TF showed a more prominent and organized layer 6, composed of medium sized cells.

Entorhinal cortex. The entorhinal cortex, ER (also area 28), is located medial to the rhinal sulcus, is readily distinguished from neighboring cortex, area 35, in Nissl and myelin stained sections. ER was characterized in Nissl by large conspicuous cell bodies in layer 2, in addition to a cell sparse band (lamina dissecans) separating the deep and superficial layers (Preuss and Goldman-Rakic, 1991b; Amaral et al., 1987). In myelin, ER was characterized by long, thick radial fibers, which were very distinct from the neighbor cortex of area 35 (ibid.).

Somatosensory cortex

Primary somatosensory cortex (3a, 3b, 1, and 2). The medial and ventro-lateral extent of S1 (areas 1, 3a, 3b and 2) based on physiology and cortical geography (cf. Pons et al., 1985; Preuss and Goldman-Rakic, 1991b) appears to be correlated with the presence of relatively dense SMI-32-ir cell label, especially in layer 3, relative to cortex further medial or ventro-lateral. These transitions are indicated in some cases by open line contours, one near the dorsal ridge of the cingulate sulcus, and one near the dorsal ridge of the lateral sulcus, sometimes extending into the dorsal bank. The areas of S1 are difficult to distinguish in the coronal plane, and are thus represented by truncated outlines where their identification was evident.

Areas 3a/3b/1. Areas 3a, 3b, and 1 were distinguished primarily by cytoarchitecture as described by Pons et al., (1985) (also see Jones et al., 1978; Jones and Porter, 1980). No portion of 3a included the larger Betz cells characteristic of area 4, though often did contain large pyramidal cells in deep layers. Similarly, in SMI-32 sections, 3a contains large layer 5 pyramidal cells, though not as large as observed in area 4.

Area 3b was distinguished from 3a in Nissl sections by its broad and dense granular layers 2 through 4, and a relatively cell free layer 5. In SMI-32 sections, 3b was characterized by a very broad supergranular band of small neurons

Area 1 contains more layer 3b and 5a medium sized cells than 3b, and was more laminated and appears columnar. Area 1 was densely packed with small SMI-32-ir cells in a broad layer 3, with apical dendrites extending through layer 2. Area 3b had less distinctive apical dendrites extending into layer 2 than did area 1. In myelin, area 1 had relatively dense staining, appearing a single thick band spanning layers 3 through 6.

Area 2. Area 2 extends from the cingulate sulcus and along the crown of the postcentral gyrus, to roughly the upper bank of the lateral sulcus. The architectonic features of this portion of area 2 that were physiologically mapped (Pons et al., 1985) were used to delineate the remaining portions of area 2 (refer to text). In SMI-32 sections, area 2 was characterized by relatively thin band of medium sized pyramidal cells in layer 3, and a sparser band of cells in layer 5 that included large pyramidal cells in some sections. In myelin stains, area 2 was relatively lightly stained with faint inner and outer bands of Baillarger, and had loosely packed, thick vertical bundles. In Nissl, area 2 showed a thin granular layer 4, a relative paucity of cells in

layers 3, but with small to medium sized cells in layers 3b and 5a that were sometimes more evident than in area 1 (Jones et al., 1978; Pons et al., 1985). Area 2 shares borders with areas 1, 5, 23, 7b, 7t, and the S2 complex. The transition between area 5 and area 2 was subtle (2 to 5 mm range), characterized by denser SMI-32-ir cell label in layer 3 of area 5. Additionally, area 5 often showed denser myelination in upper layers than did area 2.

Area 5. Area 5 extends from the cingulate sulcus, occupies the postero-medial parietal lobule, and extends down most of the anterior bank of the IPS, and out to the tip of the IPS. Area 5 was delineated predominantly from cyto- and myeloarchitecture. In Nissl stains, area 5 was characterized by often prominent medium to large pyramidal cells in layer 5 and medium sized cells in layer 3 (Jones et al., 1978). The dorso-posterior extent of the area 5 outline begins where layer 3 and 5 cells were larger and more intensely stained than in neighboring areas MDP and MIP. Larger layer 5 cells were predominantly located in anterior portions of 5, near the antero-posterior level of the precentral dimple out to near the tip of the IPS. In myelin, two bands of Baillarger are present throughout most of area 5, with moderate to dense staining overall. The thickness, density and separation of the bands varied gradually throughout portions of area 5, suggestive of multiple subdivisions.

Area 5 was divided into ventral, 5V, and dorsal, 5D, subregions. Area 5V had well separated bands of Baillarger, and was generally lighter in myelination. Area 5D was more variable in myelination throughout its extent, being denser in anterior portions, having a stronger radial component in posterior portions, and having less well separated bands of Baillarger overall than 5V. In SMI-32 sections, area 5 also showed heterogeneous label. Posterior portions of 5D were moderately to lightly populated, showing a high degree of

modularity. Along the anterior ridge of the IPS, area 5D was moderately to heavily populated with SMI-32-ir cells. Just ventral to this dense ridge region was the 5V/5D border. Area 5V showed well separated bands of SMI-32-ir label, including moderate to dense label in layer 3, and moderate label in layer 5 with often large, prominent pyramidal cells. Area 5V and 5D overlap with area PEa and PE, respectively (Seltzer and Pandya, 1986), though PEa appears to extend further posterior in the IPS, including portions or all of MIP in this study.

Area 5 borders area MIP, MDP, (31), 23, VIPm, AIP, 2, and 7t. The 5V/VIPm transition was primarily identified in myelin by two well separated bands of Baillarger in 5V, which appeared to fuse together in VIPm. Also, posterior VIPm was more densely myelinated overall than 5V, and the two areas were comparable in anterior portions. In SMI-32 sections, 5V shows two well organized and moderately to very dense bands of labeled cells in layer 3, and layer 5.

AIP. Area AIP lies along the fundus and lateral bank of IPS near the tip. AIP was defined primarily by myeloarchitecture (Preuss and Goldman-Rakic, 1991b), in which a single light band spanning layers 3 through 6 is present, though in some sections an outer band of Baillarger is evident. In SMI-32 sections, AIP was characterized by a thin band of small and medium sized neurons in layer 3, with staining that is lighter overall than neighboring cortical regions, except for VIPl. In Nissl stains, AIP often has smaller and less intensely stained cells, especially in layers 3 and 5, relative to surrounding areas 7t, 7b and 5. AIP borders areas VIPl, VIPm, LIPv, LIPd, area 5, 7t and 7b. The transition from AIP to VIPl was subtle, where VIPl was more densely labeled with SMI-32-ir cells, as well as denser in myelination. The AIP/LIPd

boundary was also subtle in some cases, wherein two moderate to light bands of Baillarger were present in LIPd.

7t. Zone 7t (possible subdivision of 7b) lies along lateral ridge of the IPS near the tip (hence 7t). This area was characterized by prominent SMI-32-ir cell label in layer 3, with sometimes lighter label in layer 5. This label was often striking relative to the sparser label of areas AIP and 7b, though the transition to areas 2 and 5 were more subtle in some cases. Zone 7t was also characterized by a relatively dense outer band of Baillarger that correlated well with the dense SMI-32-ir label, though with myelination alone this area was difficult to delineate. Borders include 2, 5, 7b, and AIP.

7op. Opercular area 7op lies along the posterior-most portion of the dorsal bank of the lateral sulcus (cf. Preuss and Goldman-Rakic, 1991b; also PGop, Pandya and Seltzer, 1982). In myelin, 7op was characterized by a moderate to light outer band, and a lighter and more diffuse inner band of Baillarger. Relative to area 7b, the inner band of 7op was generally less distinct and radial bundles were less apparent, giving 7b a more organized radial appearance overall. Cortex further anterior showed a gradual increase in prominence in the outer band of Baillarger, which was excluded from the outline, and probably belongs to the S2 complex. Area 7op had light to moderate SMI-32-ir cell label in layer 3, and was stronger than 7b. In Nissl stains, layer 3c and 5a (to a lesser extent) were often comprised of densely stained, small to medium sized cells that distinguish this region from 7b and Ri (Preuss and Goldman-Rakic, 1991b; also see Pandya and Sanides, 1973). 7op borders areas 7b, Ri, the S2 complex, and sometimes Toc.

Area S2 complex. Area S2 occupies the dorsal bank of the lateral sulcus, and portions of the superior limiting sulcus (Preuss and Goldman-Rakic, 1991b; Burton et al., 1995). The core region of S2 was characterized in myelin stains by a very dense and prominent, thick outer band of diffuse fibers. Cortex immediately posterior and medial (along the fundus) to the outlined portion of S2 most likely corresponds to the S2 complex as well, and is indicated in some cases. Cortex further anterior overlapped estimated S2 in some cases, and was often characterized by a stronger radial component merging into FPO of Preuss and Goldman-Rakic (1991b). SMI-32 label was variable throughout the S2 complex, with the core region of S2 being relatively light. Cortex along the superior limiting fundus (in estimated portions of S2) typically contained light to moderate SMI-32-ir cell label, distinguishing it from the densely myelinated region. The S2 complex borders area 7op, Ri, Ig, 2, and cortex further anterior. The S2 core region transition to 7op was gradual in myelin stains, where 7op did not contain a prominent outer band of Baillarger, and was not as dense overall. 7op showed a greater density of SMI-32 labeled cells in layers 3 and 5. Additionally, 7op had a distinct band of layer 3 cells in Nissl stains (Preuss and Goldman-Rakic, 1991b).

Ri. The retroinsular area, Ri, lies along the fundus of posterior portions of the lateral sulcus (Jones and Burton, 1976). Area Ri was characterized in myelin stains by a relatively light, single band including layers 3 through 6. In SMI-32 sections, cell label in layer 3 was moderate to light, being less densely populated than neighboring areas Toc and 7op. The location and staining of Ri was similar to that described for area CM of Morel et al., (1993). Other borders of Ri include Ig and the S2 complex, which were more subtle.

Insular cortex (Ig, Id, and Ia). The granular and dysgranular insular regions were grouped together in this study (Friedman et al., 1986; Preuss and Goldman-Rakic, 1991b). In addition to having a granular layer 4 (Jones and Burton, 1976), Ig showed a light outer band of Baillarger in myelin stains, which was lighter than that of S2, and stood out as the deeper layers of Ig were relatively sparsely stained. Dysgranular insula, Id, in addition to having a less prominent granular layer 4, showed a more lightly myelinated outer band than Ig, plus lighter myelination overall. The agranular insula and its subdivisions were grouped together in this study (Carmichael and Price, 1994).

Areas Ig and Id are bordered by the S2 complex, Pi, Ia, and cortex further ventral (not included in this study). Ig is further distinguished from the S2 complex by less dense SMI-32-ir cell label. Area Pi is distinguished from Ig/Id by much lighter myelination.

Cingulate cortex

23. The extent of area 23 and its subdivisions, occupying the posterior half of the cingulate sulcus, was primarily defined by cytoarchitecture, by its granular layer 4, and a relatively thin layer 5 cell layer (Vogt et al., 1987; Matelli et al., 1991). The 23a and 23b subdivisions were nearly devoid of SMI-32-ir cell label, while 23c contained very sparse label, contrasting with light to moderate label in cortex near the dorsal fundus of the cingulate sulcus. The location of 23c in this study (identified in some cases) largely overlapped 23c of Vogt et al., (1987), though we excluded the sulcal ridge, which was nearly devoid of SMI-32-ir cell label, and included more of the fundus region as did Matelli et al., (1991). The trend of increasing SMI-32-ir cell label density from 23a/b to 23d to M2 is consistent with Nimchinsky et al., (1996).

Area 23 borders areas 31, 30, 24, area 4, and primary somatosensory cortex. Areas 23 and 31 were difficult to distinguish in our tissue, where 31 was comprised of architectonic features intermediate between 23 and MDP. The dorsal bank of the cingulate, between 23 and primary somatosensory cortex and area 4, contained a relative moderate increase in SMI-32-ir cell label and a dense outer band of Baillarger, which was scored as a region of uncertainty. This dorsal bank may include area 6c in anterior portions at the antero-posterior level of area 4 (Akbarian et al., 1994), and somatic koniocortex in posterior portions (Skc, Matelli et al., 1991).

24. Area 24 lies along the anterior half of the cingulate sulcus, and is divided into four subdivisions, similar to Matelli et al., (1991). All divisions of 24 were agranular (or dysgranular). Area 24a is the ventral-most subdivision, bordering the callosum, and area 24b lies along the medial wall and includes the ventral ridge of the cingulate sulcus. Both 24a and 24b are nearly devoid of SMI-32-ir cell label, and those cells that were labeled were weakly stained. In myelin, 24b was moderately dense, with a prominent radial component, and two bands were often present. Area 24d was characterized by lighter myelination than surrounding cortex, with a strong tangential component. In Nissl, 24d had a thinner layer 5 band of cells than 24b. 24d was lightly populated with SMI-32-ir cells in layer 3, though lighter than cortex further dorsal. The 24d/24c transition was not marked in this study, but was characterized in Nissl by a broadening of layer 5 as described by the above authors. The subdivisions of area 24 border M2, 6DC, 23, 32, and cortex further anterior and medial (areas 8B and 9).

29/30. Areas 29 and 30 occupy a thin strip lying along the callosal sulcus (Vogt et al., 1987; Preuss and Goldman-Rakic, 1991b). These areas are bordered primarily by area 23, and were defined by cytoarchitecture.

31. Zone 31 lies between area 23 and MDP on the medial wall, having intermediate architectonic features (Vogt et al., 1987; Preuss and Goldman-Rakic, 1991b).

Motor and premotor cortex

Area 4. Primary motor cortex (area 4) outlines were defined principally by the giant, deeply stained pyramidal cells (Betz cells) in layer 5 (Jones et al., 1978). The outlines excluded surrounding cortex that showed a decreased size in the prominent layer 5 pyramidal cells. The extent of area 4 was further delimited by SMI-32-ir staining. The basal and apical dendrites of the giant layer 5 pyramidal cells were considered to be a distinguishing feature of area 4. The Betz cells and giant SMI-32-ir cells of layer 5 appeared to be the same population of cells, and were easier to identify in SMI-32 sections, in which a dense plexus of basal dendrites were evident. The area 4 transition with area 3a was further characterized by a shift from agranular (area 4) to dysgranular cortex (3a). Area 4 may extend further ventral and lateral than depicted in other studies, which was characterized by smaller Betz cells that were comparable in size to layer 5 pyramidal cells of neighboring areas 3a and 4C.

Dorsal premotor cortex (6DC, 4C, and M2). The dorsal premotor region was parceled based largely on the cytoarchitectonic scheme described by Barbas and Pandya (1987). Zone M2 included part of the dorsal bank of the

cingulate sulcus, the medial wall, and extended laterally toward the precentral dimple, though did not include the fundus of the cingulate in this study. M2 was defined in cytoarchitecture by relatively prominent medium-sized pyramidal cells in layers 3 and 5, and a lack of large and conspicuous layer 5 pyramidal cells characteristic of 6DC. In myelin, M2 shows strong radial fibers and a faint outer band of Baillarger, distinguishing it from 24d. In SMI-32 sections, M2 was moderately populated with medium sized cell bodies in layers 3 and 5, and corresponding dense dendritic plexi. In two cases, the M2 boundary with 6D (overlapping portions of 6DR of above authors) was striking, wherein lateral cortex showed much stronger label in layers 3 and 5, and correlated with the Nissl and possibly myelin boundary. M2 shares borders with 6DC, 6D, 24d, and 8B.

The zone 6DC was characterized in cytoarchitecture by the presence of a scattered distribution of medium to large sized pyramidal cells in layer 5. Myelination was moderately dense, but lacked a distinct inner band. SMI-32-ir cell label was moderate, with scattered large pyramidal cells in layer 5. 6DC together with M2 roughly correspond with 6M of Preuss and Goldman-Rakic (1991b), and the supplementary motor area (Woolsey et al., 1952). Borders of 6DC include area 4, 4C, 6D, M2, and the area 23/24 region.

Zone 4C, extending from area 4 to portions of the posterior bank of the arcuate sulcus, was primarily delineated in Nissl stained sections. The extent of 4C in this study overlapped that of Barbas and Pandya (1987), but also included a greater extent of the posterior arcuate sulcus. Myelination in 4C was denser than in 6DC, and SMI-32-ir cell bodies in layer 5 were larger than in 6DC, though smaller than the Betz-sized cells of area 4. In some cases, SMI-32-ir cell label showed distinct large layer 5 pyramidal cells that correlated

well with cytoarchitectonic features. 4C shares borders with areas 8Ac, 6Val, 6DC, and 4.

6D was distinguished from M2 by cytoarchitecture, wherein cells in layer 3 were less densely stained and less compact. In several cases, SMI-32-ir cell label in 6D (and 6Ds) was considerably denser in layers 3 and 5 relative to M2.

6Ds and 6D. 6Ds was characterized by dense myelination from the dorsal shoulder of the arcuate sulcus extending down most of the medial bank (Preuss and Goldman-Rakic, 1991a). In Nissl stains, the posterior boundary of 6Ds was demarcated by a lack of the large layer 5 pyramidal cells characteristic of bordering areas 6DC and 4C. 6D was characterized by relatively lighter myelination than 6Ds, and in some sections lighter SMI-32-ir cell label with smaller sized pyramidal cells. The 6D/6Ds border was sharp in some SMI-32-ir sections, correlating with myeloarchitecture.

6Vam. The medial subdivision of 6Va (suggested by Preuss and Goldman-Rakic, 1991a) included cortex along fundus of the ventral limb of the arcuate sulcus. 6Vam lies near the fundus of the arcuate, and is characterized by light myelination, appearing as a single band including layers 4 through 6. SMI-32-ir cell label in 6Vam was light or absent, showing distinctly less label than in the surrounding cortex. Area 6Vam may overlap area F5 of Matelli et al., (1985), and portions of area 45b of Schall et al., (1995). 6Vam borders areas 45, 8Ac, and 6Val.

6Val. 6Val, lying along the ventral ridge of the arcuate sulcus, was characterized by relatively heavy myelination, a broad and distinct outer band of Baillarger, and an inner band that often fused with the white matter

(Preuss and Goldman-Rakic, 1991a). In Nissl, 6Val did not include cortex with larger pyramidal cells characteristic of posterior bordering areas 4C and possibly 3a. However, the dense outer band appeared to continue into cortex containing the larger layer 5 pyramidal cells. SMI-32-ir cell label was relatively dense in layer 3, distinguishing it from surrounding cortex in anterior sections. 6Val borders 4C, 6Vb, 6Vam, and less distinctly with area 12.

6Vb. Area 6Vb lies along the gyrus between the arcuate and lateral sulcus, bordering 6Va, PrCO, and less distinctly with 12 and 3a/3b (Preuss and Goldman-Rakic, 1991a). 6Vb was characterized lighter myelination than surrounding cortex, and the presence of fine radial fibers. In Nissl, layer 5 was more compact in 6Vb than in 6Va, and the layer 4 band was not as well developed as in PrCO.

PrCO. The precentral opercular region (PrCO) includes the convexity dorsal to the lateral sulcus, sharing borders with areas 6Vb, G, and lying anterior to the S2 complex. PrCO is characterized in Nissl stains by a well developed granular layer 4 (Preuss and Goldman-Rakic, 1991a), and may include portions of area OFO, as defined by the above authors. In myelin stains, PrCO has a broad outer band a Baillarger...? and a strong radial component, distinguishing it from 6Vb.

Prefrontal cortex

8Ac. Area 8Ac is located along the fundus and anterior bank of the arcuate sulcus at the spur of the sulcus, bordered by areas 8Am, 8As, 46p, 45, 6P, and 6Vam. 8Ac was distinctive in myelin and Nissl (Preuss and Goldman-Rakic,

1991a), as well as in sections stained with the SMI-32 antibody. Nissl sections characterize 8Ac as having relatively large layer 5 pyramidal cells. This feature correlates with SMI-32 staining, which also demonstrates large layer 5 pyramidal cells and a relatively dense layer 3. The region of large layer 5 pyramidal cells may correspond with the location of the frontal eye fields (Stanton et al., 1989). In myelin, 8Ac appears denser than cortex further medial and lateral, correlating with Nissl borders and SMI-32-ir cell differential label. The 8Ac border with 4C was subtle in coronal sections, with 4C being denser in SMI-32-ir cell label and myelination.

8Am. Area 8Am is located along the fundus of the dorsal limb of the arcuate sulcus, and borders areas 8As, 8Ac, and 6Ds. 8Am was defined by myeloarchitecture where it is composed of tangential fibers and very few radial fibers (Preuss and Goldman-Rakic, 1991a). In SMI-32 sections, labeled cells are relatively less dense than in surrounding cortex.

8As. The cortex along the lateral bank of the dorsal arcuate sulcus has been set apart from surrounding cortex in this study, lying between areas 8Am and 8Ar. In SMI-23 sections, zone 8As was characterized by prominent label of small and medium sized cells in layers 3 and 5. The labeling did not appear well organized, giving 8As an overall diffuse appearance, especially in anterior sections. Zone 8As was more densely myelinated than 8Am, having a more distinct outer band, but did not have as strong of a radial component as 46p. 8As appears to include portions of 8Ar and 8Am described by Preuss and Goldman-Rakic, (1991a).

Area 8Ac borders 8As, and the transition is best characterized in Nissl, where 8As does not contain any prominent cells or cell clusters in layer 5

(Preuss and Goldman-Rakic, 1991a). The transition in SMI-32 was also characterized by smaller cell bodies in 8As than 8Ac.

46p. Zone 46p occupies the posterior ridges of the principal sulcus, and includes areas 8Ar, 46dr and 46vr of Preuss and Goldman-Rakic, (1991a). In myelin stains, zone 46p was characterized by a strong radial component and an overall moderately dense appearance. In Nissl stained sections, 46p had a particularly broad and prominent granular layer 4. The myelin and cytoarchitectural characteristics best defined the zone. In SMI-32 sections, 46p showed a light to moderately dense layer 3 band of small and medium sized cells. This band of label was significantly lighter than in area 45. Other borders include 46v, 46d, 8Ac, and 8As.

46v. Area 46v lies along both banks of the principal sulcus, and shares borders with areas 46p and anterior cortex not included in this study (Preuss and Goldman-Rakic, 1991a). The outline of 46v only includes cortex that is relatively lightly myelinated and in Nissl contains a prominent layer 4. In SMI-32 sections, 46p contained sparse numbers of small and medium sized cells in layers 2 and 3, while 46v was virtually devoid of label.

Area 45. Area 45 lies along the anterior bank of the ventral arm of the arcuate sulcus, bordering 46p, 6Vam and 12. Area 45 was best characterized in sections stained with the SMI-32 antibody, where the densely labeled bands of layers 3 and 5 stand out relative to the surrounding cortex. In myelin, area 45 was heavily stained with a diffuse to moderate to radial component, and stands out relative to surrounding cortex. Area 45 in this study closely matched area 45a of Schall et al., (1995), and overlaps area 45 described by Preuss and

Goldman-Rakic (1991a). Both area 45 of Carmichael and Price (1994) overlapped area 45 of this study, although their area 8 immediately ventral to 45 was generally included in the transition region between 45 and 6Vam, as opposed to an explicit outline (this portion of area 8 was characterized by moderate to light SMI-32-ir cell label). Area 45 may also extend further onto the antero-lateral surface, being characterized by moderate SMI-32-ir cell label that stood out from surrounding cortex.

G. Gustatory cortex is located along the fundus of the superior limiting sulcus, and is bordered by areas PrCO, Ia, and other cortical areas not included in this study (Carmichael and Price, 1994). In myelin stains, area G is characterized by a dense, single band of fibers with a strong tangential component, and distinct outer band. In Nissl, area G is distinguished by a densely packed infragranular layers. In SMI-32 sections, G showed an increase of density of label in the layer 3 band, which was striking in some cases. The extent of area G was truncated relative to the borders shown by above authors, as we excluded the lighter myelinated tails.

Frontal cortex (10, 11, 12, 13, 14, 32, 25). The areas and subdivisions of frontal cortex were defined with the cyto- and myeloarchitectonic features and differential SMI-32-ir cell label described by Carmichael and Price (1994).

Auditory-related cortex

A1 and R. The primary auditory field, A1, and the primary-like rostral field, R (Morel et al., 1993), were grouped together as one region in this study. A1 was characterized in myelin by a dense band covering layers 4 through 6, and

was not separated from the white matter. In Nissl, A1 was identified by a broad and densely packed layer 4. In sections stained with the SMI-32 antibody, A1 showed a very prominent thick band of medium and small pyramidal cells in layer 3, and a lighter distribution of small cells in layer 5. This band of label stood out from the much lighter stained medial and lateral regions.

Acetylcholinesterase staining patterns in two cases verified the location of these regions (ibid.).

Pi. The parainsular region, zone Pi, lies along the floor and banks of the inferior limiting sulcus (Jones and Burton, 1976). The zone Pi in this study was most readily identify in myelin sections, where the staining density overall was much lighter than surrounding cortex. A medial-posterior portion of Pi was particularly light in myelin stains, having only few fibers in deep layers. A line is drawn in most cases to indicate this region in most cases. The remaining portions of Pi had fibers evident in upper layers, sometimes forming a distinguishable outer band. In Nissl, Pi had a granular appearance overall, no sublamination in layers 5 and 6, and layer 3 was often distinct. Zone Pi overlapped areas Pro, pal, and proA of Galaburda and Pandya (1983), all of which lie within the circular sulcus. Pi bordered Ig/Id, A1/R, and Ia.

Tpt. The temporal parietal area, Tpt, is located at the temporal lobule (Preuss and Goldman-Rakic, 1991b). In Nissl stains, Tpt was characterized by a columnar appearance, especially layers 3 and 5. In myelin, Tpt had a stronger radial component than surrounding cortex, and moderately dense overall. This area has a light band of SMI-32-ir cells in layer 3, which distinguishes it from the heavier label in Toc and TPO. Tpt also borders area ST.

Toc. Zone Toc (temporal opercular, caudal) occupied the ventral bank at the posterior-most extent of the lateral sulcus. In myelin stains, Toc was characterized by relatively dense overall staining with a matted appearance. Toc showed very little if any separation between the inner and outer bands of Baillarger in most sections, distinguishing it from Tpt and 7op. The transition from Toc to A1 was characterized by an increase in density of myelination, especially in the lower band of Baillarger (Morel et al., 1993). In SMI-32 sections, Toc was characterized by a broad and relatively dense layer 3 band of medium sized pyramidal cells. This staining characteristic was also evident in A1, but denser. Thus, the transition from A1 to Toc was gradual in most cases. Toc may correspond to the postauditory zone C of Morel et al., (1993), and to area T3 of Akbarian et al., (1994). Toc shares borders with A1, Ri, 7op, Tpt, and sometimes 7b/7a.

ST. Area ST (also Ts) lies along the crown of the temporal gyrus (Preuss and Goldman-Rakic, 1991b), and borders Tpt, L, and sometimes A1/R. ST was characterized in myelin by two thin and moderately dense bands with a slight radial component. In SMI-32 sections, ST was very sparsely labeled or devoid of label relative to surrounding cortex, having small to medium sized pyramidal cells lightly distributed in layer 3. Tpt was distinguished from ST in Nissl sections, where Tpt showed a clear columnar organization not present in ST (Preuss and Goldman-Rakic, 1991b). Anterior portions of ST were not analyzed, and dorso-medial portions may include area L of the above authors, though not explicitly represented.

Chapter 3: Cortico-cortical Connections of Visual, Sensorimotor, and Multimodal Processing Areas in the Parietal Lobe of the Macaque Monkey

ABSTRACT

We have studied the cortico-cortical connections of architectonically defined areas of parietal and temporo-parietal cortex, with emphasis on areas in the intraparietal sulcus (IPS) that are implicated in visual and somatosensory integration. Retrograde tracers were injected into selected areas of the IPS, superior temporal sulcus (STS) and parietal lobule. The distribution of labeled cells was charted in relation to architectonically defined borders throughout the hemisphere and displayed on computer-generated three-dimensional reconstructions and on cortical flat maps.

Injections centered in area LIPv led to connections mainly with extrastriate visual areas, whereas injections centered in VIPl and VIPm led to progressively stronger connections with somatosensory, polysensory, and motor areas. Injections of VIPl and VIPm produced moderate to strong projections with similar but not identical constellations of roughly 30 of the architectonic areas identified in all lobes of the hemisphere, plus sparser connections with many additional areas. Sensorimotor projections were predominantly from the hand, arm, and possibly face representations of at least 8 somatotopically organized areas or regions, including areas 1, 2, S2, 5V, 4, 24d, M2 (supplementary motor area), and premotor cortex in and near the posterior end of the arcuate sulcus. The visual-related connections of VIPl overlapped the patterns seen in LIPv injections. Additionally, LIPv and MSTdp were found to have similar patterns of connections throughout the

hemisphere, both in distribution and relative strengths. These and results from injections into other parietal areas support the fine-grained partitioning of cortical areas described in Chapter 2, and indicate the presence of multiple highly distributed hierarchical networks involved in multimodal integration.

INTRODUCTION

Cortical regions outside of primary sensory areas and areas not devoted to specific sensory or motor functions have classically been considered "association" areas, wherein information from different modalities is integrated. It has become increasingly clear that regions of overt multimodal integration occupy relatively restricted portions of the cortical surface. Various cortical areas along and near the intraparietal sulcus are thought to be major contributors to the integration of the visual and somatosensory modalities, based in part on physiological and anatomical studies. Physiological recordings in the intraparietal sulcus (IPS) have revealed several sensory and perhaps motor-related areas. In posterior and lateral regions of the IPS, cortical areas are mostly visual-related, being part of the dorsal stream visual pathway (Ungerleider and Mishkin, 1982). These areas are high in the visual cortical hierarchy, and predominantly receive inputs from other visual areas of the dorsal stream (Baizer et al., 1991; also see Felleman and Van Essen, 1991). In anterior portions of the IPS (such as area 5), cortex is somatosensory-related, with many neurons being responsive to various aspects of complex arm and hand movements (Sakata et al., 1973), and predominantly connected with somatosensory and somatomotor cortex (Jones et al., 1978; Vogt and Pandya, 1978; Pearson and Powell, 1985; Burton and Fabri, 1995). In addition to sensory-related functions, some areas of the IPS are involved with movement-related activities as well as higher cognitive processes. These include attention and intention, generating eye movements (area LIP, Andersen, 1995; Colby et al., 1996), and reaching and hand manipulation movements (area 5, Mountcastle et al., 1975).

Roughly between the above visual- and somatosensory-dominated regions lies a swath of cortex whose constituent cells share properties of both modalities. The bimodal properties observed thus far suggest that at least portions of the IPS have a role in visually guided reaching and grasping movements (Leinonen and Nyman, 1979; Taira et al., 1990), mouth and lip manipulation (Leinonen and Nyman, 1979; Duhamel et al., 1997), vestibular and visual integration that may involve comparisons of head and eye movements (Graf et al., 1996), and eye-hand or eye-hand and mouth coordination, as occurs during feeding behaviors (Colby and Duhamel, 1991).

Studies of cortical connections provide general support for the above physiological findings. For example, cortex along or near the fundus of the IPS receives converging inputs from both visual and somatosensory areas (Seltzer and Pandya, 1980; Pandya and Seltzer, 1982). Additionally, several studies involving tracer injections in other cortical regions have shown light to moderate connections with fundal regions of the IPS from somatosensory cortex (Vogt and Pandya, 1978; Pons and Kaas, 1986), visual cortex (Van Essen et al., 1980; Colby et al., 1988; Boussaoud et al., 1990), and motor/premotor cortex (Leichnetz, 1986; Tanné et al., 1995). However, we have only a fragmentary understanding of the relative strengths and precise distributions of inputs to portions of the IPS relative to the numerous architectonically defined areas throughout the hemisphere. Furthermore, it is not clear how those inputs from visuotopically and somatotopically areas are integrated in cortex where they directly converge in the IPS. Recent physiological studies of the ventral intraparietal area (VIP), located along the middle third of the fundus of the IPS, have found tactile and visual receptive fields that match. For instance, neurons with visual receptive fields in the upper hemifield or quadrant are often correlated in size and location (and direction selectivity) with tactile

receptive fields on upper portions of the head and face, while the lower visual receptive fields are correlated with hand and arm and lower portions of the face and neck (Duhamel et al., 1997). Beyond this relationship, no clear topographical organization has been observed in VIP.

A detailed understanding of the connectivity of intraparietal areas has been difficult to attain for a variety of reasons, including the general difficulty of making restricted injections in areas that are small in dimensions and buried deep in sulci that often contain irregular folds. This is exacerbated by the fact that these areas are high in the visual and somatosensory hierarchies, 4 to 8 levels up from their sensory inputs--they are mainly connected with areas which themselves are not well understood, and tend to lack robust architectonic boundaries (Andersen et al., 1990; Blatt et al., 1990; Van Essen et al., 1990).

The analysis of cortico-cortical connectivity presented here capitalizes on the revised and refined architectonic partitioning scheme for parietal cortex and other regions of the hemisphere described in Chapter 2. In addition, we analyze connections using computational neuroanatomical methods that allow interchangeable visualization in multiple formats, including slices, three-dimensional reconstructions, and flat maps. With this approach, we studied the connections of newly identified architectonic zones, including VIPl, VIPm, and MSTdp, with the aim of ascertaining whether their connection patterns are sufficiently distinct to warrant calling them distinct cortical areas. We also provide a more detailed analysis of the connections of areas previously studied, including LIPv, AIP, 7a, 7b, and MT.

Some of these results have been presented as abstracts (Lewis and Van Essen, 1994, 1996).

MATERIALS AND METHODS

Results were obtained from 6 cases analyzed in detail (each with multiple injections) and supplemented by results from an additional 5 cases. All were from juvenile macaque fascicularis monkeys (6 females and 5 males) weighing 2.0 to 3.8 kg. After mapping the sulcal geometry of the IPS and/or STS, restricted injections of two to three retrograde neuronal tracers were placed into separate locations, with most of the injections aimed at deep lying cortical areas VIPl, VIPm, and LIPv (see Table 1 below). The location of injection sites and location of labeled cells throughout the ipsilateral hemisphere and portions of the contralateral hemisphere were charted in series of coronal or near-coronal sections. These connectivity patterns were related to architectonic subdivisions identified in nearby sections stained for myelin, Nissl, and SMI-32 immunoreactivity (Chapter 2).

Surgical procedures

Surgical procedures were conducted with strict aseptic technique, and included an initial chamber implant, physiological mapping of cortical gray matter plus the injection of tracers, and an optional electrophysiological mapping of portions of somatosensory cortex. For surgical preparations, animals were tranquilized with an initial dose of ketamine HCl (10 mg/kg i.m.), and premedicated with atropine (27 mg/kg i.m.) or glycopyrolate (11 mg/kg i.v.), dexamethasone (0.27 mg/kg i.v.), and cephalothin (25 mg/kg i.m.). Surgical anesthesia was induced with isoflurane (2-5%) in air containing 2.5% CO₂. The heart rate, expired CO₂, and rectal temperature were monitored and maintained within appropriate physiological limits for surgical

anesthesia throughout the operative procedure. Following recovery surgeries, animals were maintained for approximately one week on a regimen of antibiotics (cephalexin 25 mg/kg twice daily) and analgesics (buprenex, 0.1 mg/kg, and aspirin). All procedures were performed according to protocols approved by the Animal Study Committee at the California Institute of Technology and Washington University.

Chamber implant and tracer injections. A stainless steel chamber was implanted over the parietal lobe of one or both hemispheres, centered 1-2 cm lateral to the midline and 2-3 cm anterior to the occipital ridge (approximately over the IPS for a 3 kg monkey). In a separate surgery (after a one week recovery), cortex overlying the IPS and in some cases the STS was exposed with one to three skull openings (1 - 2 cm² total). Skull opening and dura openings sizes were minimized to reduce post-operative trauma to the underlying cortex. Upon reflecting the dura, the cortical surface was photographed to facilitate cortical mapping. A custom made manipulator and microdrive were secured to the chamber. The chamber was filled with mineral oil and sealed, which helped to reduce brain pulsations. The sulcal folds of the IPS and/or STS were mapped by electrophysiological recording of spontaneous, multiunit activity, using Tungsten electrodes (A-M Systems, Inc.; 0.005 mm core, 10 MW). This mapping allowed the determination of structural boundaries including gray versus white matter and lumen gaps in the sulci. After estimating the locations of desired cortical target sites, two or three retrograde tracers were injected at separate locations in each animal. The retrograde tracers were Fast Blue (FB, Sigma Co. 5% aq.), Diamidino Yellow (DY, Sigma Co. 3% aq.), and WGAapoHRP-Gold (AG, 0.7% aq., Menetrey, 1985). The

WGAapoHRP-Gold tracer was prepared as described by Basbaum and Menetrey (1987).

Tracers were injected using customized triple barreled glass pipets (A-M Systems Cat #6090): One barrel was loaded with a tracer, and the other two with 0.5M NaCl, which allowed for physiological recording to verify the location of the pipet tip in cortex. Injection volumes ranged from 50 to 250 nl for each tracer. To reduce tracer leakage along the pipet track, the glass pipet was held in place at the cortical target site for 15-30 minutes prior to injection. Tracer was then slowly injected with an air pressure system (PV830 Pneumatic Picopump, World Precision Instruments), and allowed to stand for an additional 30 minutes before retracting the pipet. Animals recovered for an 11 to 21 day period following the tracer injections. There followed an electrophysiological mapping experiment and/or euthanasia and intracardial perfusion (refer to Chapter 2).

Data analysis, architectonics, and unfolding

Sections were cut at 60 μ m thickness on a freezing microtome, and stored refrigerated in 0.1M phosphate buffer. Blocks were cut in the coronal plane (10 hemispheres) or orthogonal to the IPS (3 hemispheres). Every sixth section was used for viewing the WGAapoHRP-Gold and Fluorescent tracer labeling. The remaining sections were used for histological processing, as described in Chapter 2.

In sections analyzed for labeled cells, gold particles from the WGAapoHRP-Gold tracer were developed in one or two cycles with a silver enhancement kit (Ted Pella Inc., silver enhancing kit Cat# 15719). Free floating sections were washed in dH₂O (5 to 10 min), incubated in the silver enhancement solution

(10 to 30 min), washed again, returned to 0.1M phosphate buffer, and mounted on glass slides coated with gelatin-chrome alum. This development procedure did not interfere with the fluorescent tracers, allowing all three tracers to be viewed in the same tissue sections.

Retrogradely labeled cells were viewed using a fluorescence microscope (Zeiss, Axioplan). Using the computerized neuroanatomy software MDPlot (Minnesota DataMetrics, version 3.0), data were plotted onto this set of sections (tracer sections), including fiducial alignment marks, approximate sulcal and fundal boundaries, pial and layer 4 contours, retrogradely labeled cells, and injection sites. Methods for transferring architectonic borders and generating flat maps are described in Chapter 2. Retrogradely labeled cells were assigned 3D coordinates and an identity according to the type of label. Each cell was projected to the nearest tile in the three-dimensional surface reconstruction of layer 4 (cortical blocks were represented by up to 90,000 tiles). By preserving this geometrical relationship, cells could be positioned on the flat maps relative to the nearest tile. In some regions of cortex, labeled fields from two or three tracers would overlap, obscuring some labeled cell types. For illustrations, the positions of cells over the cortical flat maps were layered, such that the cells of one identity (such as all the DY labeled cells) could lie below or above all the cells of another identity (FB or AG labeled cells).

Tracer injection analysis

The effective uptake zone of a tracer injection was evaluated based on inspection of sections containing the injection site and halo of intense diffuse labeling. Additionally, pipet tracks were examined for possible tracer leakage.

Table 1 summarizes the injections of this study, including the size of the injection bolus, the area or areas included in the estimated effective uptake zones, and survival times for each case. The amount of tracer effectively taken up and transported in one injection versus another was difficult to quantify, despite knowing the approximate volume of the injection bolus and the tracer concentrations. Thus, a qualitative gradation of estimated strengths was assessed in each case based on the relative density and total number of cells labeled throughout the hemisphere or cortical block. In most cases, this estimate was positively correlated with the injection bolus volume.

For illustration on flat maps, outlines of the extent of the injection core, halo, and the pipet track were projected to the nearest layer 4 contour and processed in the same manner as described for architectonic boundaries (Chapter 2). Tracks passing through white matter were not projected onto the cortical flat maps, but rather are implied by the presence of a gap between the point of entry and the injection site.

TABLE 1. List of Experiments¹

Case	Tracer	Injection size	Layers	Estimated ² uptake zones (%)	Survival (days)
A (94CR)	FB	s m	3-5	LIPv::95	14
	DY	l g	1-4	VIPl:LIPv::80:20	
	AG	3X sm	all	7a/7b::100	
B (95DR)	FB	med	all	AIP::70	19
	DY	med	all	VIPm:VIPl::90:10	
	AG	l g	1-3	MSTdp::85	
C (93IR)	FB	l g	3-6	LIPv:VIP::85:15	14
	DY	med	1-4	LIPd:7a::60:40	
D (94EL)	FB	med	all	MT::100	17
	DY	med	all	MT:MSTp::90:10	
E (94IR)	FB	med	all:2-3	VIP:LIPv	19
	DY	med	1-4	VIP:AIP::80:20	
	AG	med	1-4	7a:LIPd::40:60	
F (93GR)	FB	l g	all	VIP:5V::50:50	11
	DY	s m	1-4	VIP?	
<u>Cases not illustrated:</u>					
G (94GR)	FB	l g	2-6	VIP:LIPv:LIPd::40:50:10	13
H (95AR)	DY	med	all	AIP:7b::80:20	21
I (95BR)	DY	s m	4-6	MT::95	17
J (95CR)	DY	s m	all	MT::95	16
K (95GR)	FB	m d	1-5	VIP:LIPv::60:40	15

¹DY, Diamidino Yellow; FB, Fast Blue; AG, WGAapoHRP-Gold; sm, small (50 to 90 nl); med, medium (80 to 150 nl); lg, large (140 to 250 nl). ²Estimates are based on presence of tracer within the core outline of each area.

RESULTS

Overview. Most of the desired target zones in this study are small (1 to 3 mm wide), making it difficult to obtain injections entirely restricted to a single area. The results are derived from 4 injections of retrograde tracers restricted to one cortical area or zone (estimated 90% or better), 5 injections largely restricted to one area (80% - 90%), and 11 tracer injections that included more than one area or zone (Table 1). Our analysis concentrates on comparing the cortico-cortical connections of deep lying areas of the IPS with those of other parietal or visual areas. Six cases (A - F) comprising fifteen tracer injections are illustrated below. Each injection yielded complex patterns of label across large portions of the hemisphere. We will discuss each injection in relation to overall cortical geography, and with respect to architectonically identified areas. Additional data from other cases are summarized in Table 4 at the end of this section.

Briefly, the results that follow illustrate several findings. First, area VIP (VIPl and VIPm subdivisions) has widespread connections, including distinct portions of motor and somatosensory cortex (hands, digits, arm, and face representations), with visual cortex (with hints of topographic organization), and several bimodal or polysensory areas. Second, both AIP and 7b (7a/7b) show similar connectivity patterns to VIP from sensorimotor-related cortical areas (again overlapping hand, arm, and face representations), but differ in the degree and location of inputs within such areas. Unlike VIP, these areas receive little visual input, except from higher visual areas and possibly bimodal or polysensory areas. Third, visual-related connections of LIPv are similar to those of VIP (mostly VIPl), with the notable exception of V3, which projects more heavily to LIPv than VIP. Together, these data illustrate the

complex patterns of inputs into portions of the IPS that subserve multimodal integration.

Case A. Case A included a relatively large DY injection centered in VIPl, illustrated in Figures 1 and 2, plus a small FB injection restricted to LIPv and a triplet of small AG injections placed along the surface of area 7b, which are both illustrated in Figure 3. Figure 1 uses three formats to illustrate the pattern of DY labeling in relation to cortical geography, including a three-dimensional (3D) reconstruction, a smoothed 3D surface, and a cortical flat map. Figure 2 represents portions of a select series of sections, highlighting connections of particular interest, which also serves to orient the reader to the layout of the flat map representation.

Figure 1A shows a micrograph of a Nissl stained section including the injection core, which was centered in the fundus of the IPS. Figure 1B shows the stack reconstruction of two layer 4 contours from closely spaced coronal sections (360 μ m) containing the DY injection core. These sections are also illustrated in Figure 2 (Panels F and G), in which the injection core is blackened and the injection halo plus tissue damage from the pipet are outlined. The injection site is also represented on a flat map in Figure 1F. As indicated by the track outline, the approach to VIPl was through the cortex of 7b/7a, LIPd, and LIPv. Some tracer label was present in the VIPl/LIPv transition region and in layers 1 and 2 of LIPv, though the latter was deemed to be relatively minor.

Figure 1C and 1D show the antero-posterior level of the sections containing the injection core, as well as the resulting distribution of DY labeled cells on lateral and medial views of a three-dimensional (3D) reconstruction of most of the right hemisphere. Only cells not obstructed by

cortical folds and above the layer 4 surface are visible. In these views, multiple clusters of labeled cells are evident, including extensive labeling in the IPS, moderate labeling in the central, arcuate, lateral, superior temporal, and parieto-occipital sulci, and light labeling in the cingulate sulcus. Labeled cells in buried regions can be more readily seen in a highly smoothed representation (Panel E), and better still in the flat map (Panel G). In Panels C through H, the surface is shaded to show mean curvature, thereby conveying a distinction between sulcal folds (dark streaks) and gyral folds (light streaks). On the flat map, retrogradely labeled cells are shown in two shades of green, with cells above the layer 4 surface (supragranular layers) shown in light green and cells below the surface (infragranular layers) shown in dark green. The infragranular layer cells were made visible by projecting them above rather than below the flat map surface.

In Figure 1G, the overall pattern of DY cell label included three large swaths of retrogradely labeled cells, one involving parieto-occipital cortex (middle to upper left on map), another in occipito-temporal cortex (lower center), and a third in frontal cortex (upper right). The parieto-occipital swath included dense label in both banks of the IPS, plus moderate labeling further posterior in occipital cortex, in more medial and lateral parts of parietal cortex, and extending into the parietal operculum of the lateral sulcus (sylvian fissure). The occipital-temporal label included both banks of the STS, mostly along the posterior half. Label in the frontal lobe included a major swath extending from the central sulcus, across the arcuate and into posterior principal sulcus, plus sparse label along the medial wall and into the cingulate sulcus.

In relation to major functional subdivisions, the labeled fields involved many areas of somatosensory, motor, visual, and polymodal cortex. Heavy to

moderate label resulting from the VIP1 injection included areas known or presumed to be visual (LIPv, LIPd, PO, PIP, LOP, 7a, MSTda, and MSTdp), several polymodal (VIPm, MIP, MDP, 7b, Toc, TPO subdivisions), somatosensory (area 5V, the S2 complex, 7op, 3a), motor and premotor (areas 4, 4C, 6Vam, 6Val, M2, and area 24 subdivisions). The projections from MSTda and TPOc appeared as a continuous labeled field, which correlates with the similarity of SMI-32-ir architecture observed in these areas (Chapter 2). Within visual areas that are topographically organized, including V2, V4, and PO, cells were predominantly located in lower, peripheral visual field representations (V2, Gattass et al., 1981; V4, Gattass et al., 1988; PO, Colby et al., 1988); only sparse label was present in VP (upper visual field representation; Newsome et al., 1986). Some cell label was located near the ventral tip of MT, but outside its core region, which may correspond to a central visual field representation (Desimone and Ungerleider, 1986; Maunsell and Van Essen, 1987).

Within several somatotopically organized areas, labeled cells were predominantly located in regions estimated to represent the arm and hand representations (and possibly the face representation), including areas 4, 4C, and surrounding premotor cortex (Woolsey, 1952; Rizzolatti et al., 1981a,b; Sessle and Wiesendanger, 1982; Godschalk et al., 1984), and M2 (F3 of Luppino et al., 1991, 1993), and also the arm, hand, and/or digit representation of areas 24d (Luppino et al., 1991), 3a, 1 and 2 (Pons et al., 1985). Label within the core outline of the S2 complex corresponds with the estimated digit and hand representation (Burton et al., 1995). This pattern of label supports the physiological organization of bimodal response properties of VIP (Duhamel, 1997), wherein some cells containing lower visual field representations are also responsive to tactile stimulation to the hand, arm, trunk and lower face regions (as opposed to the upper face and head).

Figure 1. Illustration of the DY injection of case A. (A) A micrograph of a Nissl stained section that included the injection core. (B) Layer 4 contour outlines of sections containing the DY injection core. (C, D). 3D maps showing distribution of labeled cells. Only cells above the layer 4 surface are visible. (E) Lateral view of a highly smoothed 3D surface, serving as an intermediate representation to the flat map. (F) Illustration of the injection site on the flat map, where green outlines depict the core (dark green), halo (medium green), and injection track damage (light green). The light gray outline near area 7b depicts tissue compromised by the skull opening. (G) Flat map representation of the VIP1 centered injection and distribution of retrogradely labeled cells (21,326 DY labeled cells plotted). The tip of the frontal lobe and temporal lobe were excluded from the block, and area V1 was removed after reconstruction. Additionally, two cuts were introduced to reduce surface distortions (dashed lines). The flat map contains 90 architectonically identified areas or regions. Details regarding areal boundary outlines and identification are presented in Chapter 2 (Case 94CR). In the STS, $da = MSTda$, and $m = MSTm$. In the arcuate sulcus, $m = 8Am$, $s = 8As$. (H) Distribution of DY label in a portion of the contralateral hemisphere (oriented as a right hemisphere to facilitate comparison). Scale in micrograph is 1 mm, other scales and cross bars are 1 map-cm.

Figure 2. Distribution of DY label on coronal sections from case A. Upper left inset corresponds to Figure 1C, and shows the approximate location of the 13 sections (A-M). In the coronal sections, solid lines represent the pial surface and gray/white matter boundary, and dashed lines represent the layer 4 contour. Each dot corresponds to one retrogradely labeled cell. Some areal boundaries are indicated by bars in the white matter (other excluded for clarity). Scale is 1 cm.

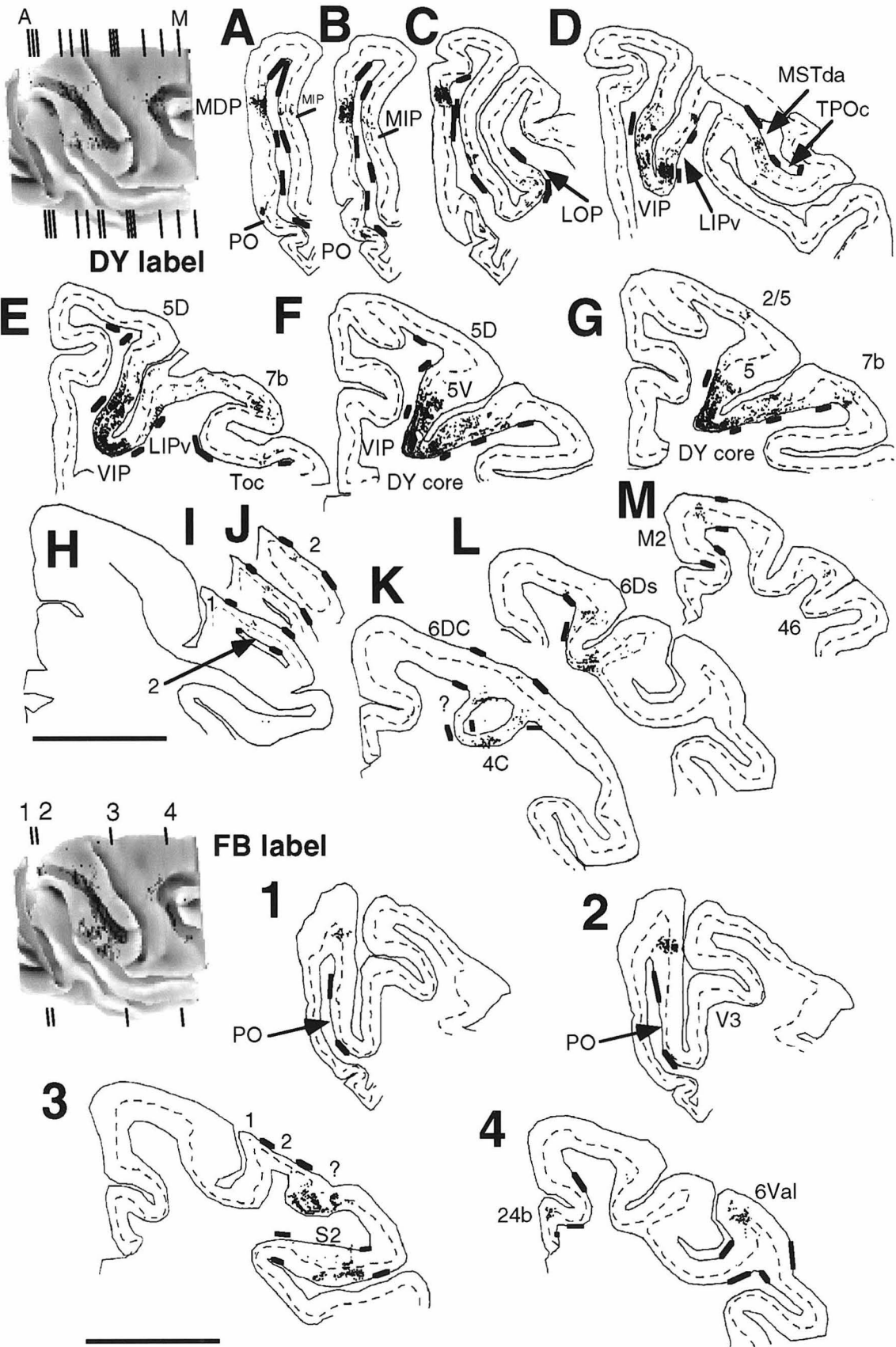


Figure 3. Illustration of the FB (LIPv) and AG (7b) injections of case A. (A - D) Distribution of FB, and AG labeled cells on the 3D layer 4 reconstruction. Middle insets show sections containing the FB and AG injection cores. (E) Flat map showing injection sites and the distribution of retrogradely labeled cells of FB (4,115 cells) and AG (10,899 cells). The AG tracer was difficult to score in this case, thus the distribution of label represents a lower bound representation of the connections. (F) Expanded view of the FB, AG and DY injection sites on the flat map representation. The AG injection site consists of three small Au injections clustered on the surface of the parietal lobe in area 7b. The FB injection of LIPv was approached through the cortex of 7a and LIPd, and the core was centered 3 mm away from the DY injection core. FB label in the IPS of the contralateral hemisphere (not shown) was concentrated in layers 2/3 and 5 of LIPv, with few cells in the cortex surrounding the core outline. Scale bars are 1 cm, and scale cross is 1 map-cm. Other conventions as in Figure 1.

In the contralateral hemisphere of case A (Fig. 1H), the distribution of DY label was, as expected, heaviest in the anterior half of VIPl, geographically homotopic to the injection site. Heavy label was also present in the anterior half of VIPm, which was homotopic with portions of the injection halo. Moderate label was present in areas LIPv and TPOc, in addition to lighter label in MSTdp, MIP, PO, 5V, LIPd, the 7a/7b region and possibly the S2 complex. Light label was also present in MDP and anterior portions of TPO (not shown).

Within the various architectonic zones and areas delineated in this hemisphere, 5 or more labeled cells (i.e., exceeding a very sparse connection density for sensitive tracers) were present within the core extent of 44 areas and zones. As expected, the density of labeled cells in different areas varied greatly, as indicated in Table 2. We distinguished 5 pathways scored as dense (+++), 15 as moderate (++), and 24 as light (+) or (+?). Some areas with very sparse label (<5 cells) within the core region are categorized as questionable ('?') (also see Table 4).

Three characteristic laminar patterns of retrograde label are distinguished in Table 2, and illustrated in Figure 2. Labeled fields that were distributed predominantly in supragranular layers (>70%) are denoted by an 'S'. These included areas V4 (dorsal), PO, area 1, area 2, and possibly dorsal V2, PIP, V4ta, area 4, and Toc. These are characteristic of feed-forward projections (Rockland and Pandya, 1979; Maunsell and Van Essen, 1983). Labeled fields predominantly in infragranular layers (>70%) were denoted by an 'I', and included areas 24d, M2, the S2 complex, 5D, 7b, Ig/Id, and possibly TPOi, LOP, and 6D, and are characteristic of feed-back projections. Most of the labeled fields shown in Figures 1 and 2 had a bilaminar distribution, denoted by a 'B' in Table 2, with 30-70% of the cells in superficial layers and the rest in deep layers. In some areas the laminar distribution was uncertain ('?'), either due

Table 2. Summary of connections for VIPI of case A. Refer to text for details.

Regions	MIP	LIPv	VIPl	VIPm	5V	5D	MDP	7t	S2cx	7b	7a	LIPd	AIP	7op	Ig/Ild	Toc
Strength	+++	++*	***	+++	+++	++	++	++	++	++	+	++	+	+	+	+
Laminae	B	B	B	B/I	B/I	I	B	B	I	I	B	B	B	I?	I?	S/B
Regions	PO	LOP	PIP	V2d	VP	TPOc	MSTda	MSTrr	MSTdp	MT	FST	V4ta	V4d	ITd	TPOi	TPOr
Strength	++	++	++	+	+	+++	++	+	++	+	+	+	+	+	++	+
Laminae	S	I?	S/B	S/B	?	B	?	?	B	B	B	S/B	S	B	I?	I?
Regions	4	4C	8Ac	24a,b	24c	3a	1	2	6Val	6Varr	M2	46p	46v	6Ds		
Strength	++	++	++	+	+	+	+	+	+	+	+	+	-	+		
Laminae	S/B	B?	B	B	B	B	S	S	B	B	I	B		?		

to sparse data or cells lying just outside of the core of the architectonic subdivisions. The bold type in Table 2 indicates pathways that have not previously been reported or where uncertain. Additionally, only those pathways that were consistent across other injections are indicated in bold (also see Table 4).

Figure 3 shows results for the other 2 injections in case A, with blue representing the small FB injection centered in LIPv, and red representing the AG injections centered in 7b. There was very little overlap between label associated with the LIPv and 7b injections. In contrast, each of them overlapped markedly with the DY label from the VIPl injection (Fig. 1G). These patterns of label are displayed on the flat map so that the FB (blue) occludes AG (red) in regions where there is overlap (see methods).

Labeling from the LIPv injection, though restricted due to the small effective tracer uptake, was similar to that reported by Blatt et al., (1990), and included predominantly visual areas in the occipital, parietal, and temporal lobe, and arcuate sulcus. Compared to visual-related connections of the VIPl injection, the LIPv injection included relatively stronger connections with areas V3 and MT, and weaker connections with LOP, PIP, and polymodal areas TPOc and MIP. Very little label was found in sensorimotor areas (except possibly 5V). The close proximity of the LIPv and VIPl injections (relative to the LIPv/VIPl transition) underscores the differences in the organization of inputs to the respective areas.

The pattern of label resulting from the 7b injection was similar to that reported by Neal et al., (1986, 1987) and Cavada and Goldman-Rakic, (1989b). As with the above studies, heavily connected areas included sensorimotor and polymodal cortex, and very little visual-related cortex. As with the VIPl injection, strong to moderate projections to 7b originated from MDP, anterior

portions of VIP and LIPv, portions of 7b, area 4C and cortex further ventral in the arcuate sulcus. Additionally, sensorimotor projections to 7b tended to originate from the digit, hand and arm representations (and possibly face) of areas 2, the S2 complex, and premotor 4C. DY and AG label near the fundus of the lateral sulcus (between 7op, Ri, and the S2 complex) may lie within parieto-insular vestibular cortex (PIVC), which contains cells responsive to vestibular, visual, and somatosensory stimulation (Grüsser et al., 1990). Other regions with light overlap included 7op, TPOr, 6Vam and 6Val. In contrast with the VIPl injection labeled fields, area 7b projecting cells were more heavily concentrated in the S2 complex and Ig/Id complex. Areas projecting to 7b but not VIPl included 6Vb and PrCO.

Several areas and zones contained labeled fields from two or three of the tracer injections in addition to those mentioned above. The degree to which the labeling patterns overlap provide important clues that may relate to function. For example, the densely myelinated regions TPOc and neighboring MSTda contained a tight cluster of nearly continuous DY cell label. TPOc included cells projecting to 7b, VIPl, and LIPv (with a possible somatosensory to visual gradient), consistent with the polysensory functions associated with this region. Zone MSTda contained LIPv and VIP projecting cells but not 7b projecting cells, consistent with the visual function reported for this area (Desimone and Ungerleider, 1986; Boussaoud, 1990).

In the intraparietal sulcus, overlap of all three tracers occurred in anterior portions of areas LIPd, LIPv, VIPl, VIPm, and cortex posterior to AIP, in the vicinity of a region implicated in visually guided grasping-related behavior (Taira et al., 1990; Jeannerod et al., 1995). In the frontal lobe, all three tracers overlapped in the vicinity of area 8Ac, and to a lesser extent in zone 6Vam. Together with area 45 (which contained light DY and AG cell label

overlap), these areas overlap the medial and lateral frontal eye fields (Schall et al., 1995; also see Chapter 2). Other regions that contained light to moderate overlap of the three tracers, included areas 46p, TPOi, IPa, and possibly FST.

Case B. Case B included a DY injection centered in VIPm, an AG injection centered in MSTd, and a FB injection including AIP and surrounding cortex along the lateral bank near the anterior third of the IPS. Figures 4 and 5 illustrates the DY injection centered in VIPm. The injection core (Fig. 4A, B, F, and Fig. 5F, G) was restricted to layers 1 through 6 of VIPm, and the injection halo extended into supragranular layers of VIPl. Panels C and D show the distribution of retrogradely labeled cells on lateral and medial views of the reconstruction, respectively. Panel F illustrates the injection track and approach to VIPm, through the cortex of 7a, LIPd, across the lumen of the IPS, and through the transition region of VIPm and 5V.

As with the VIPl injection of case A, the VIPm injection of case B led to three large swaths of retrogradely labeled cells, one in parieto-occipital cortex, another in occipito-temporal cortex, and a third in frontal cortex, which are visible in the 3D reconstructions (Figs. 4C and 4D) and the flat map (Fig. 4E). The parieto-occipital swath was the densest, including both banks of the IPS plus limited portions of cortex more posterior in occipital cortex, plus an extension to the medial wall, and an extension into the parietal operculum of the lateral sulcus. The occipito-temporal label was relatively light, and was mainly on the dorsal bank of the posterior STS. Label in the frontal lobe included the ridges of the posterior arcuate sulcus, and the principal sulcus, plus scattered label extending to the medial wall and into the cingulate sulcus. With regard to functional divisions, the labeled fields included many areas of

somatosensory, motor, visual, and polymodal cortex. Substantial label (>5 cells) was present in the core extent of 32 areas, as summarized in Table 3.

The labeled fields resulting from the VIPm injection of case B (Fig. 3) included many areas that were also labeled after the VIPl injection of case A (Fig. 1). In visual-related cortex these areas included LOP, PO, the parieto-occipital confluence (possibly PIP), LIPd, LIPv, other portions of VIPl and VIPm, MSTda, MSTm, MSTdp, FST, and ventral occipital cortex in or near VP. However, in contrast with the VIPl injection of case A, the projections to VIPm in case B originate from the upper peripheral visual field representations of some visuotopically organized areas, including label in medial portions of PO (Colby et al., 1988), and light label in the estimated location of VP (Newsome et al., 1986), but no label in V2 or V4. Connections with ventral portions of LOP (upper portions of LOP on the flat map) may suggest a peripheral upper visual representation in this zone. Additionally, relative to the VIPl injections, the VIPm injection of case B resulted in little or no label in several visual-related areas, including the core region of V2, PIP, V4ta, MT, MSTdp, and ITd. Also, label throughout the STS was relatively lighter overall for the VIPm injection.

Label in somatotopically organized areas from the VIPm injection showed several differences from the VIPl injection. In Figure 3, significant DY label was not present in area 4 or 3a, and also not present in the estimated digit and hand representations of the S2 complex (Burton et al., 1995). Additionally, label in M2 was more concentrated in the estimated face representation and less in the arm (F3, and possibly F7 of Luppino et al., 1991, 1993). However,

Figure 4. Illustration of the DY injection centered in VIPm of case B (95DR). (A) A Myelin stained section containing the DY core. (B) Layer 4 contours of two coronal sections (stacked) containing the DY injection core. (C, D) Lateral and medial view of 3D layer 4 surface reconstruction. Only cells in supragranular are visible. Lines indicate the location of coronal sections containing the injection core. (E) A flat map representation of the DY injection illustrating the distribution of retrogradely labeled cells (19,397 cells plotted) relative to geographic and architectonic boundaries. In the reconstruction for case B, the frontal lobe and tip of the temporal lobe were absent from the block, area V1 was removed, and one cut was introduced (dashed lines) to reduce surface distortions. The map shows over 80 architectonically identified cortical areas/regions. Blue, red and yellow dots near the tip of the IPS depict physiologically mapped cortex, overlying the digits representation of somatosensory cortex (see Chapter 2: Fig. 19). (F) Flat map representation of the injection core, halo, and track damage. Scale in panel A is 1 mm, and other scales are 1 cm. Other conventions as in Figure 1.

Table 3. Summary of connections for VIPm of case B. Conventions as in Table 2.

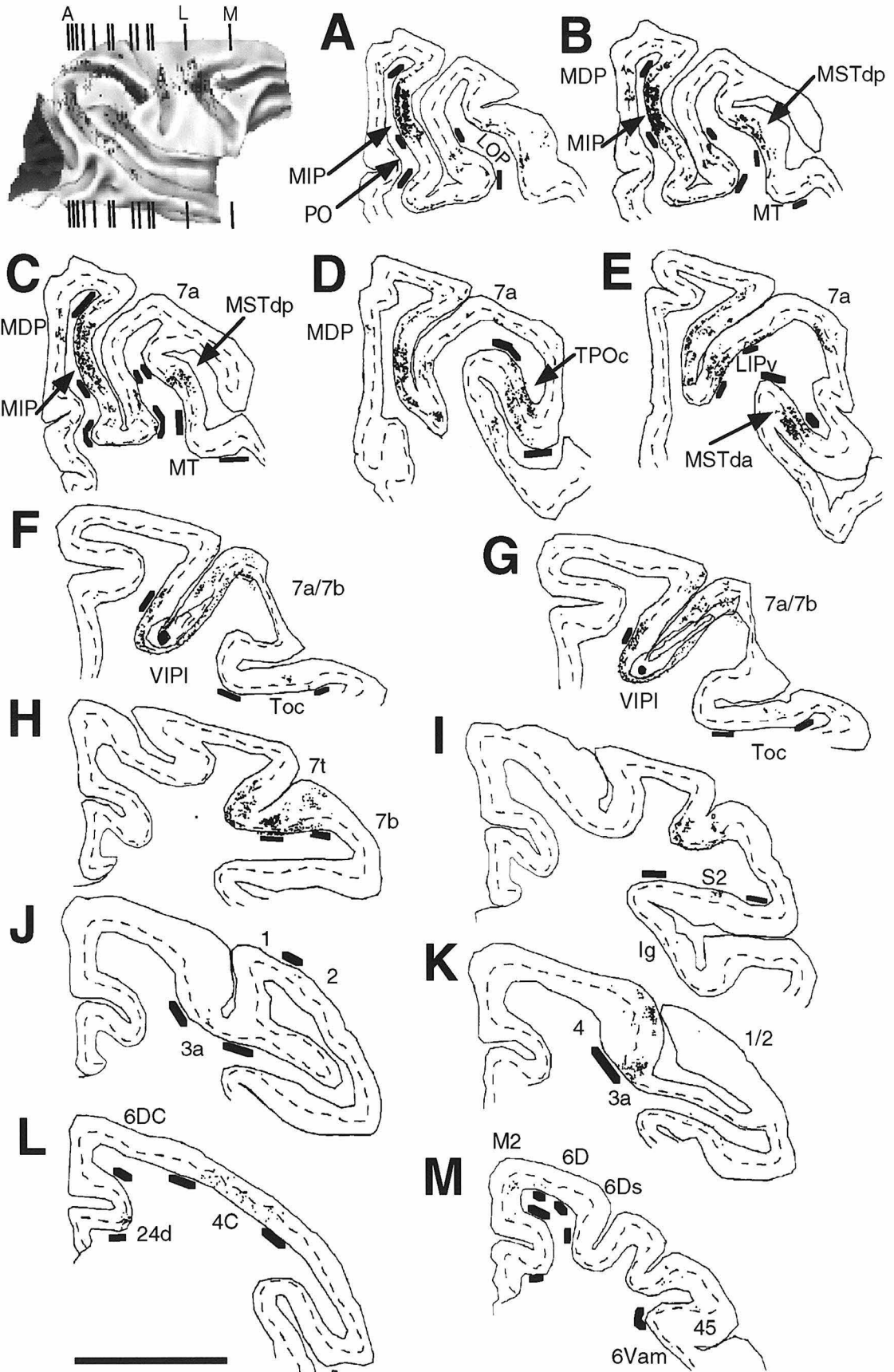
Regions	MIP	LIPv	VIPI	VIPm	5V	5D	MDP	7t	S2cx	7b	7a	LIPd	AIP	7op	lg/lid	Toc
Strength	++	+++	+++	***	++	+	+++	+	+	+++	-	++	+	+	?	+
Laminae	B	B			B	?	B	S?	I	B		?	B	?		B
Regions	PO	LOP	PIP	V2d	VP	TPOc	MSTda	MSTm	MSTdp	MT	FST	V4t	V4d	ITd	TPOi	TPOr
Strength	++	+	?	-	+?	++	++	+	?	-	+	?	-	-	+	?
Laminae	S	S			S	B	I/B	B	?		?				?	I
Regions	4	4C	6Varr	6Val	8Ac	24d	24a,b	3a	1	2	M2	46p	46v	6Ds		
Strength	-	++	+	+	++	+	+	-	?	+	+	+	+	++		
Laminae		B	I	?	B?	?	I			S	I	I	?	B		

similar to the VIPI injection of case A, light label was present in area 2 (Fig. 5H-I) close to the digit 1 and face representation, based on physiological recordings (Chapter 2), and possibly in the estimated arm representation (lateral to the post-central dimple: Pons et al., 1985). Label was also present in the arm representation of 24d (Luppino et al., 1991). Connections with 4C showed similar patterns of dense connections in the two cases, though the topography based on cortical geography was difficult to compare. The global pattern of connections appears to support the organization of somatosensory and visual receptive fields in cells of area VIP suggested by physiology (Duhamel et al., 1997). In particular, the portion of VIP of case B received relatively stronger face representations (as opposed to the overall stronger hand and arm representation inputs shown for the VIP injection of case A) and also received inputs from the upper visual field representation of several visual areas.

Patterns of label common to the VIPI and VIPm injections were also present in several polysensory areas, including TPOc, TPOi, Toc, 7b, MIP, and MDP, and somatosensory and motor areas 7op, 24a/b, 6Ds and cortex along the posterior portion of the arcuate sulcus. Label in MDP in the VIPm injection of case B was very dense and concentrated (Fig. 5A-C), and also prominent in the contralateral hemisphere (see below). This projection was consistent with connection studies of MDP (dorsal 7m), which was found to receive inputs from the medial fundal region of the IPS (area IPd of Seltzer and Pandya, 1986; Cavada and Goldman-Rakic, 1989b). In the frontal lobe, projections to the VIPm injection were absent from areas 4 and 3a, in contrast to the VIPI injection, a difference with possible functional implications.

The laminar organization of VIPm connections (Table 3, Fig. 5), suggest feed-forward projections from PO and area 2 (consistent with the VIPI

Figure 5. Distribution of DY and FB label on coronal sections from case B (95DR). Upper left inset corresponds to Figure 4C (VIPm injection), and shows the approximate location of the 13 sections (A-M) plus the distribution of DY label. The lower left inset corresponds to Figure 6A (AIP injection), and shows the location of 4 sections (1-4) plus the distribution of FB label. Panel 4 and L correspond to the same section, contrasting the DY and FB labeled fields in premotor cortex. For clarity, only portions of each section show architectonic parcellations (lines along white matter and pial surface contours). Scales are 1 cm. Other conventions as in Figure 2.



injection), LOP, the VP region, and possibly 7t. Feed-back projections originated from the S2 complex and M2 (consistent with VIPl), and also 6Vam, 46p, 24a/b, and TPOr.

Figure 6 shows results from the AG injection centered in area MSTdp and a FB injection centered in AIP. The cells are displayed such that the blue (FB) occludes the red (AG) in regions of overlap. The AG injection included layers 1 through 4 of area MSTdp, which was approached via superficial portions of area V4 (mostly layer 1), and cortex dorsal to MT. There was no indication that the pipet track crossed the lumen of the STS into TPOc, though uptake in this area may have occurred (see below).

AG label was present predominantly in visual-related regions of cortex, and overlapped many regions and areas in common with LIPv injections (Figs. 3 and 8). Extensive labeling was found across five swaths of cortex, including the parieto-occipital confluence (upper left), ventro-medial portions of temporo-occipital cortex (lower left), the posterior half of the STS (center of map), the depths of the IPS (upper center), and dorsal portions of frontal cortex (upper right). Projections to MSTdp were observed from the core extent of 31 architectonically defined areas. This pattern of label was similar to results from MST injections in other studies (cf. Boussaoud et al., 1990). Although the injection site came close to architectonically defined MT, there was no detectable label anywhere in V1, indicating that there was no significant tracer uptake into MT (Desimone and Ungerleider, 1986; Maunsell and Van Essen, 1987). MSTdp is likely to correspond to the V2 projection zone observed by Ungerleider and Desimone, (1986a).

Label from the AG injection was present in a number of topographically organized visual areas that contain upper field as well as lower field representations. These included dorsal and ventral V2, V3 and probably VP

(Gattass et al., 1981; Newsome et al., 1986), the lower visual field representation of PO (Colby et al., 1988), dorsal and probably ventral portions of V4, and possibly upper and lower field portions of V3A (Gattass et al., 1988). Overall, connections were slightly stronger with lower versus upper peripheral visual field representations.

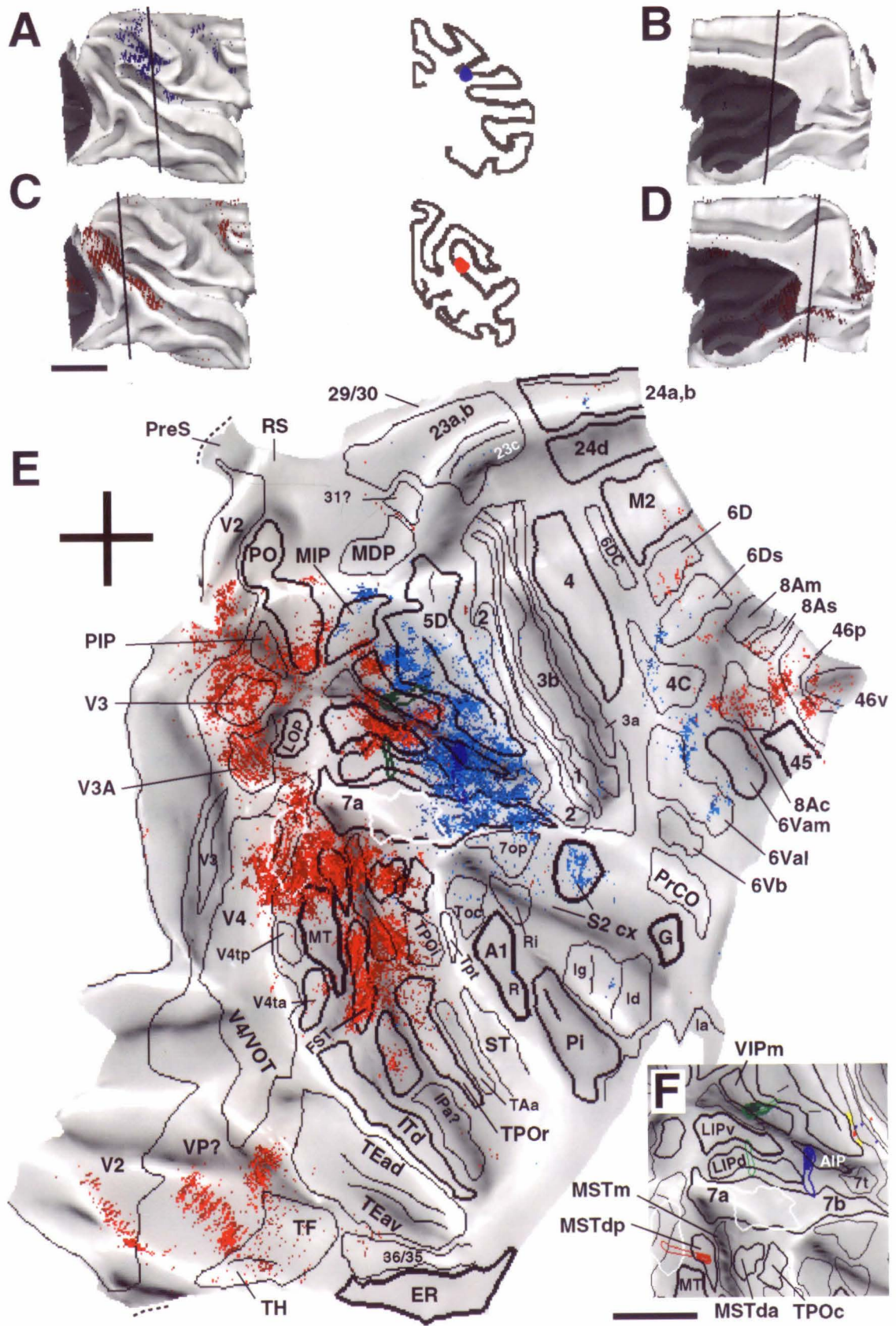
In the STS, posterior and anterior portions of MSTm contained heavy labeled fields, with a gap intervening, suggesting a possibly subdivision. The labeled field in posterior MSTm and MSTda may correspond to physiologically defined MSTd of Komatsu and Wurtz (1988), while the labeled field in anterior MSTm and the MSTm/TPOi transition region may correspond to MSTl. A notably strong projection from FST almost completely fills the core extent of this area, respecting the lateral, posterior and anterior borders, but extends across the medial border into MSTm, and more lightly into TPOi, TPOr and IPa (mostly infragranular layers).

In the IPS, notably strong label was present in LIPv, and moderate clusters of labeled cells were present at the anterior and posterior extremes of VIPm.

The anterior labeled field in VIPm was nearly continuous with the label in anterior LIPv and VIPl, and together ended gradually near the core region of AIP, respecting this border transition. The posterior labeled field of VIPm spanned the MIP/VIPm transition region, and included the ventral portion of MIP. Near the arcuate sulcus, label was located mostly along the anterior bank, in areas 8Ac, and extending dorsal into 46p, and 46v in the principal sulcus.

Regions of overlap of label from the MSTdp and VIPm injections largely involved visual-related cortex, including moderate label in 8Ac and portions of area 46p and 46v, and lighter label in PIP, VP, and MST. A feed-forward pattern of label for the MSTdp injection is present in areas V2, and possibly V3

Figure 6. Illustration of the AG and FB injections of case B (95DR), and the resulting distribution of retrogradely labeled cells. (A-D) Lateral and medial views of the 3D reconstruction showing FB and AG label (above the layer 4 surface). Middle insets show sections containing the FB and AG injection cores. (E) Flat map illustrating the distributions of cell label resulting from the AG (30,704 cells) and FB (11,330 cells) injections. Some area labels were omitted for clarity. (F) Flat map depicting the DY, FB and AG injection cores, halos, and track damage. Scale bars and cross are 1 map-cm. Other conventions as in Figure 3.



and VP. A feed-back pattern was evident in TPOc, TPOi, TPOr, IPa, TF and TH, and more lightly in area 36.

The FB injection core of case B fell largely within area AIP, including all layers, but significant leakage was evident along the pipet track in a transitional region and possibly encroaching on 7b and/or LIPd. This injection produced strong label within the IPS, moderate label along the lateral sulcus and the posterior ridge of the arcuate sulcus, and light label along the medial wall. Relative to functional areas, FB label was present in digit, hand and arm (and possibly face) representations of several sensorimotor areas. In parietal cortex, the heaviest label was present in 5V, 7t, and 7b. Label in the latter two regions may overlap an extended face representation (Leinonen and Nyman, 1979). Moderate label was present in caudal MIP, and appeared nearly continuous with label straddling MIP and cortex further posterior. This latter region may overlap area V6A of Galletti et al., (1996a) (also see Fig. 5, panels 1 and 2). Light to moderate label was present in 5D and anterior portions of LIPv, LIPd, and VIPm. Light label was present overlapping areas 1, 2 and 5 near the estimated arm, wrist and hand representations (Pons et al., 1985). In the lateral sulcus, moderate label was present along the dorsal bank of the S2 complex (Fig. 5, panel 3), which was likely to overlap the digits/hand and face representations (Burton et al., 1995). Sparser label was distributed in 7op, Ri, Toc, and in the Ig/Id complex. Label in anterior portions of the hemisphere was concentrated along the posterior ridge of the arcuate sulcus, including areas 6Val (Fig. 5, panel 4), 4C, and lightly with 6Ds, consistent with connections of premotor cortex (Godschalk et al., 1984). Light to moderate FB label was also present in 24b and 46v.

Overlap of label from the AIP and VIPm injections was moderate to light in sensorimotor cortex near the arcuate sulcus, lateral sulcus, and IPS. In

posterior portions of the lateral sulcus, FB and DY partially overlapped in areas 7op and the auditory-related zone Toc. In parietal cortex, label overlapped heavily in 5D, 7b, and 7t. Lighter overlap was present in area 2 (plus areas 1 and 5) ventral to the precentral dimple, corresponding the estimated hand, wrist, and arm representation (Pons et al., 1985).

Despite the large degree of overlap resulting from the AIP and VIPm injection labeled fields, differences in connections with premotor cortex plus several other visual and somatomotor-related areas lends some support for the distinction between a reaching-related network and grasping-related network, as described by Tanné et al., (1995, 1996). For instance, AIP has moderate connections with ventral premotor area 6Val (Fig. 5, panel 4), which is involved in grasping behaviors (Tanné et al., 1996), and also with the dorsal bank of the S2 complex, overlapping the hand and digit representations (Burton et al., 1995). This connection with S2 is consistent with functions involving grasping (versus reaching) per se. Conversely, VIP was more heavily connected with 6Ds (dorsal premotor), which is involved with reaching behaviors (Tanné et al., 1995). Also, VIP was relatively more heavily connected with MIP, which is known to contain cells involved in visually-guided reaching (Colby and Duhamel, 1991).

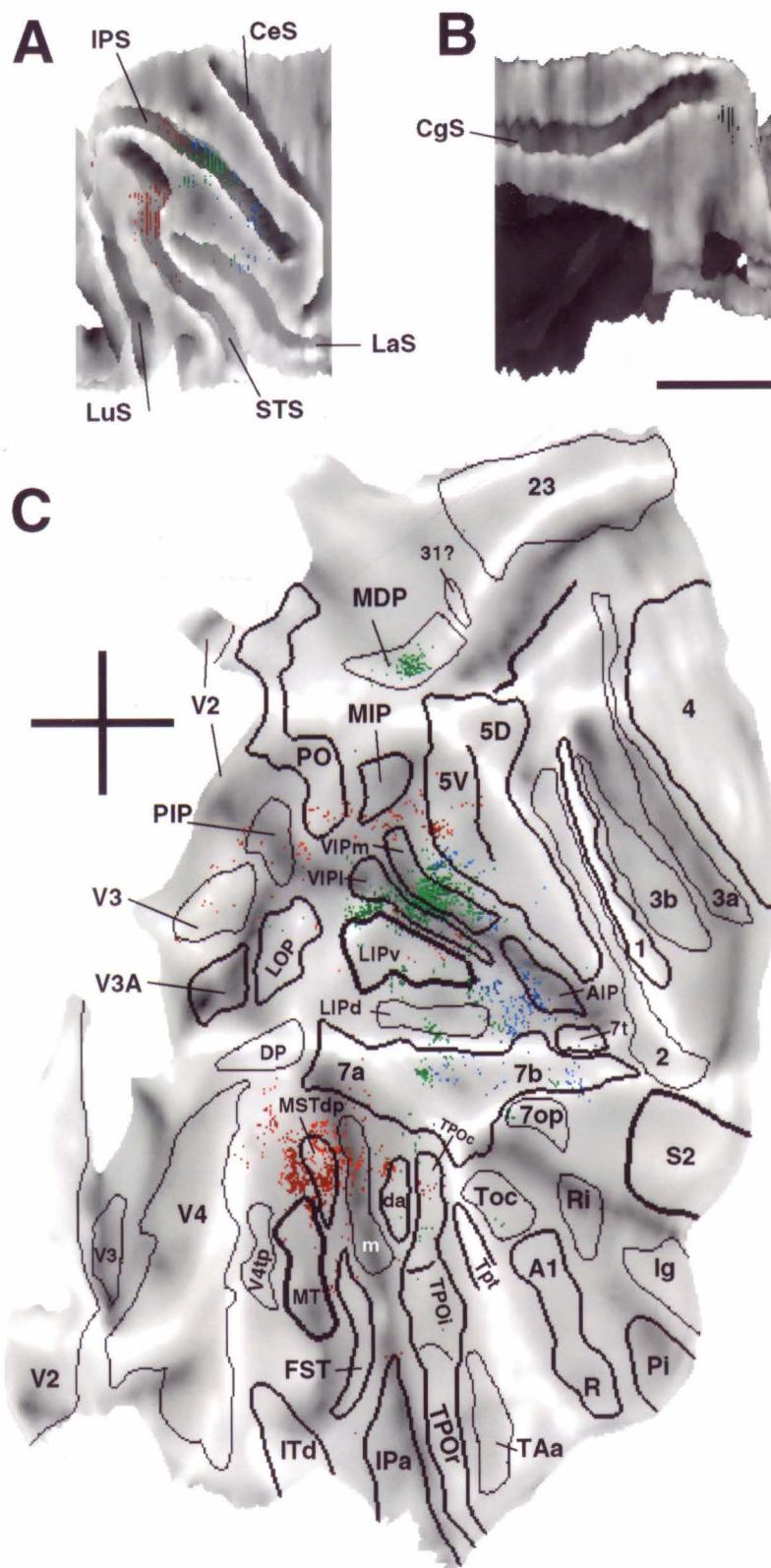
Overlap of all three tracers included several regions, reflecting areas of somatosensory and visual convergence, and included MIP, anterior portions of LIPv, LIPd, and VIP, the S2/Ri/7op transition region, portions of the posterior arcuate sulcus, M2, and 24a/b (and very lightly in TPOc). Inputs to area MIP from somatosensory AIP were located in the dorsal half of MIP (top portion on map); those from visual area MSTdp (though possibly some TPOc input) were concentrated in ventral portions; and those from bimodal area VIPm covered its full dorso-ventral extent. This pattern of label was consistent with the

functional gradient within area MIP observed physiologically by Colby and Duhamel (1991). Anterior portions of VIPm and LIPv contained overlap of all three tracers, with dense DY label and moderate FB and AG label. Consistent with these inputs, this region may correspond to cortex involved in visual guidance of hand movements (Taira et al., 1990; Jeannerod et al., 1995). Light AG, DY, and FB label in deep layers of cortex near the fundus of the posterior portions of the lateral sulcus (lying between 7op, S2, and Ri) may correspond to parieto-insular vestibular cortex (Grüsser et al., 1990), described earlier. Light label was also present in motor-related frontal areas 24a/b, 6D, 6Ds, and near the face representation of M2 (Luppino et al., 1991).

Figure 7 shows the distribution of label in the posterior portion of the contralateral hemisphere of case B from all three tracers. Evident in the flat map (panel C), the densest labeled fields for each tracer was located in regions that were geographically homotopic with the injection sites in the ipsilateral hemisphere. Additionally, the patterns of label in the contralateral hemisphere for all three tracers showed similar relative strengths to label in the ipsilateral hemisphere. However, the distribution of label was more restricted to areas that were heaviest in the ipsilateral hemisphere.

DY label in the contralateral hemisphere predominantly included bimodal, polymodal, and higher visual areas. Outside of the dense label in VIPm and VIPl, relatively strong and concentrated label was present in MDP, and moderate to light label was distributed in areas 7a/7b, LIPv, LIPd, TPOc, and Toc. Similarly, the interhemispheric connections of the AIP injection were predominantly with higher somatosensory areas, including areas AIP, 7b, 7t, and 5V (and absent from areas 1, 2, and portions of area 5 (5D) and the S2 complex). AG label outside the MT/MST complex was present in V3, PIP,

Figure 7. Distribution of contralateral cell label from FB (348 cells), DY (1809 cells), and Au (1152 cells) injections of case B (95DL). Flat map and insets are oriented as a right hemisphere to facilitate comparisons. Scales are 1 map-cm. Other conventions as in Fig. 1.



(though not V2 or V3A), PO, TPOc, and possibly MIP. Label in TPOc was predominantly in infragranular layers, suggestive of a feed-back projection.

Case C. Case C included two tracer injections, a relatively large FB injection centered in LIPv, and a large DY injection involving areas LIPd and the 7b/7a region. The results from this case are useful for visualizing the global patterns of inputs to LIPv (versus 7b/7a and LIPd), providing support for several architectonic distinctions, and comparing labeled fields with the connections of VIP in the previous two cases. In Figure 8, the FB injection core was largely contained within LIPv, though the injection extended into the LIPv/VIP transition region in layers 1 and 2. The resulting pattern of label overlapped that shown for the smaller LIPv injection in case A (Fig. 3), but the label was more robust.

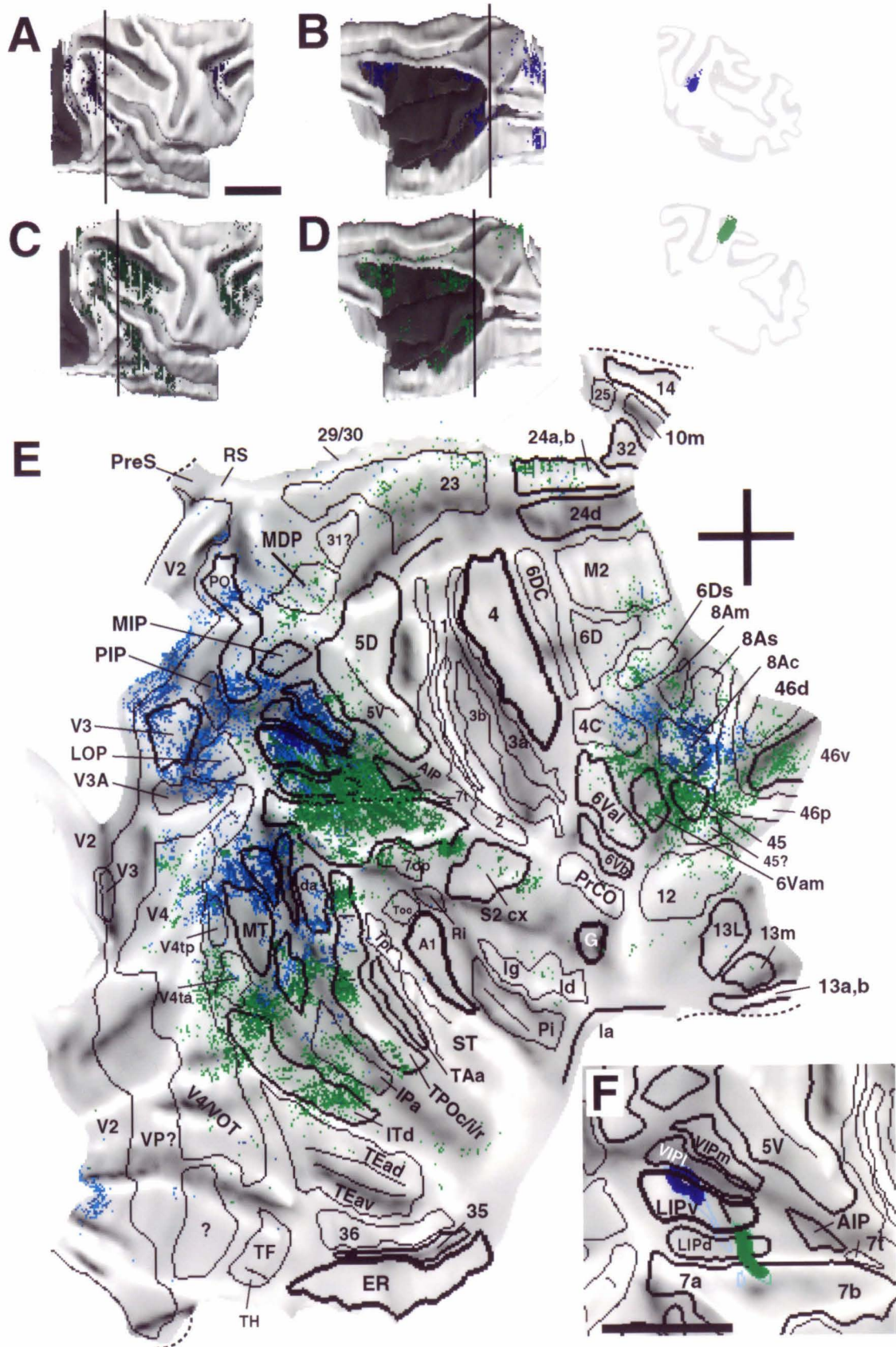
The pattern of FB label was similar that reported for LIPv by Blatt et al., (1990), being present predominantly in five visual-related regions, including posterior portions of the IPS, heavy label in the parieto-occipital region (left-most and upper left), posterior portions of the STS, the posterior arcuate and principal sulci (right-most), and lighter label in ventral portions of occipito-temporal cortex (lower left). Relative to architectonic areas, the FB injection produced label in 29 areas and zones. Label was present in a number of topographically organized visual areas, with a greater emphasis on the lower peripheral visual field representation. Moderate to heavy projections were from dorsal and ventral V2 and from V3 (lower visual field representation), lower and possibly upper field portions of V3A (Gattass et al., 1988), and both the upper and lower visual field representations of PO (Colby et al., 1988), dorsal V4 and more lightly in ventral V4 (Gattass et al., 1988), posterior portions of MT and V4tp (Desimone and Ungerleider, 1986). Relatively light

projections originated from the VP region (upper visual field representation). Additionally, label was present throughout much of areas LOP and PIP.

Also consistent with the findings of the above authors, we did not find significant projections from TF to LIPv, suggesting that this is not a reciprocal pathway. Projections from V2 to LIPv were not reported by Blatt et al., (1990), though are prominent in this case. V2 projections to VIP (mostly VIPl) were generally light to sparse, and thus it is unlikely that uptake in VIPl would explain the presence of heavy V2 label. Rather, this pattern suggests that V2 projections to the VIPl/LIPv transition region may be patchy, such that some injections reveal strong projections while others do not (also see Table 4). In the IPS, transported label from the LIPv injection was extensive throughout most of the core of VIPm, and much of VIPl, but was absent or sparse in adjoining polymodal or somatosensory-related areas 5V, AIP, and MIP. In the STS, FB label was densest in dorsal (peripheral) MT, MSTdp, and the nearby transition region. Separate moderate labeled fields were also present in FST, MSTda, TPOc, and IPa.

Along the arcuate sulcus, moderate to light projections to LIPv originated from a cluster of neighboring areas, including 8Ac, 8As, 4C, 46p, and 45. FB label is strongest in 8Ac, which is likely to correspond to the medial frontal eye fields: This region is implicated in large-amplitude saccades, and is connected with peripheral representation of retinotopically organized areas (Schall et al., 1995), which is consistent with the other FB labeled fields of this injection. Light labeled fields are also present in area 24b and the estimated face representation of M2, though this label may be due to uptake into VIPl, as they were not consistent with other LIPv injections (Table 4 below). Feed-forward projections to the FB injection originated from areas V2, V3, and possibly VP, while feed-back projections arose from areas in the arcuate

Figure 8. Illustration of the FB and DY injections of case C (93IR). (A-D) Lateral and medial views of the cortical block analyzed, showing the distribution of FB and DY retrograde cell label (only showing cells above the layer 4 surface), and corresponding insets depict location of the injection cores. (E) Distribution of FB (13,542 cells) and DY (19,986 cells) cell label on a flat map representation. FB label occludes DY label in regions of overlap. Portions of the frontal lobe and V2 were not included in the original block, and V1 and the tip of the temporal lobe were removed after reconstruction. Two cuts were introduced along the medial wall (dashed lines). The map contains 75 architectonically identified areas and regions (some labels omitted for clarity). (F) Expanded view of the injection site core, halo and pipet track for both injections. Scales are 1 map-cm. Other conventions as in Figure 1.



sulcus, including 8Ac, consistent with the hierarchical placement of LIPv (Andersen et al., 1990).

The overall pattern of FB label in the LIPv-centered injection showed many similarities to that shown for the MSTdp-centered injection of case B (Fig. 4). Both the LIPv and MSTdp patterns of label overlapped considerably in the five regions addressed above for LIPv, suggesting that these two areas are involved with similar functions. A major difference between the two patterns is the presence of strong MSTdp projections from ventral occipito-temporal regions, including VP and V4/VOT, though this may in part be due to the specific location of the injections within their respective areas. However, the moderate projections from TF/TH to MSTdp contrasts with the lack of a TF/TH to LIPv projections (mentioned earlier). Also, moderate projections from the core of LOP were present after the LIPv injection, but not from the MSTdp injection. Overlap is present in the face representation of M2 (SMA or F3, Luppino et al., 1991), 24b, and the 6Ds/6DR region.

The pattern of DY label resulting from the 7a/7b/LIPd injection in case C was consistent with previous studies (Blatt et al., 1990), and contrasts with injections of LIPv and VIP. Extensive DY label covered four swaths of cortex; one in parietal cortex, one in the mid-portion of the STS, another along the posterior end of the arcuate sulcus, and a sparser one stretching along the medial wall and cingulate sulcus. In the IPS, DY label was present in VIP and LIP, but absent from posterior visual areas such as PIP and LOP. Also, DY label was very dense surrounding the caudal portions of AIP, but was sparse within the core outline, supporting the architectonic boundary. In the STS, DY label was concentrated in mid-portions of the sulcus, including areas V4ta, FST, ITd, IPa, and TPOr. DY label was also present near foveal representations of V4t, V4, and possibly MT, in contrast to the more peripheral involvement of the LIPv

labeled fields in this case. Label in ITd included two foci with a center-to-center separation of roughly one centimeter, which may correspond to areas PITd and CITd of Van Essen et al., (1990). Two foci are also evident in area TPOr, separated by roughly 8 mm.

Along the arcuate sulcus, DY and FB label covered the posterior and anterior banks. DY label was considerably stronger in areas 45 and 6Vam, while FB label is stronger in 8Ac (see above). Together, areas 45 and 6Vam may correspond to the lateral frontal eye fields (chapter 2), which is implicated in generating small amplitude saccades, and receives input from foveal representations of retinotopically organized areas (Schall et al., 1995). This pattern of label is consistent with the DY label being present in foveal representations of V4, V4t (V4ta), and possibly MT. Other regions of overlap included frontal areas (mostly oculomotor) 4C, 8As, 46p, and possibly 6Ds. In the posterior STS, DY label was heavy in TPOc and TPOi, while sparse in MSTda, which was the reverse of the FB labeling from the LIPv injection. In Figure 8, the region of FB and DY label overlap in M2, 6Ds, and 24b was similar in location to labeled fields resulting from the three injections of case B (VIPm, AIP, and MSTdp, Figs. 4 and 6), and of two injections from case A (VIPl and 7b, Figs. 1 and 3).

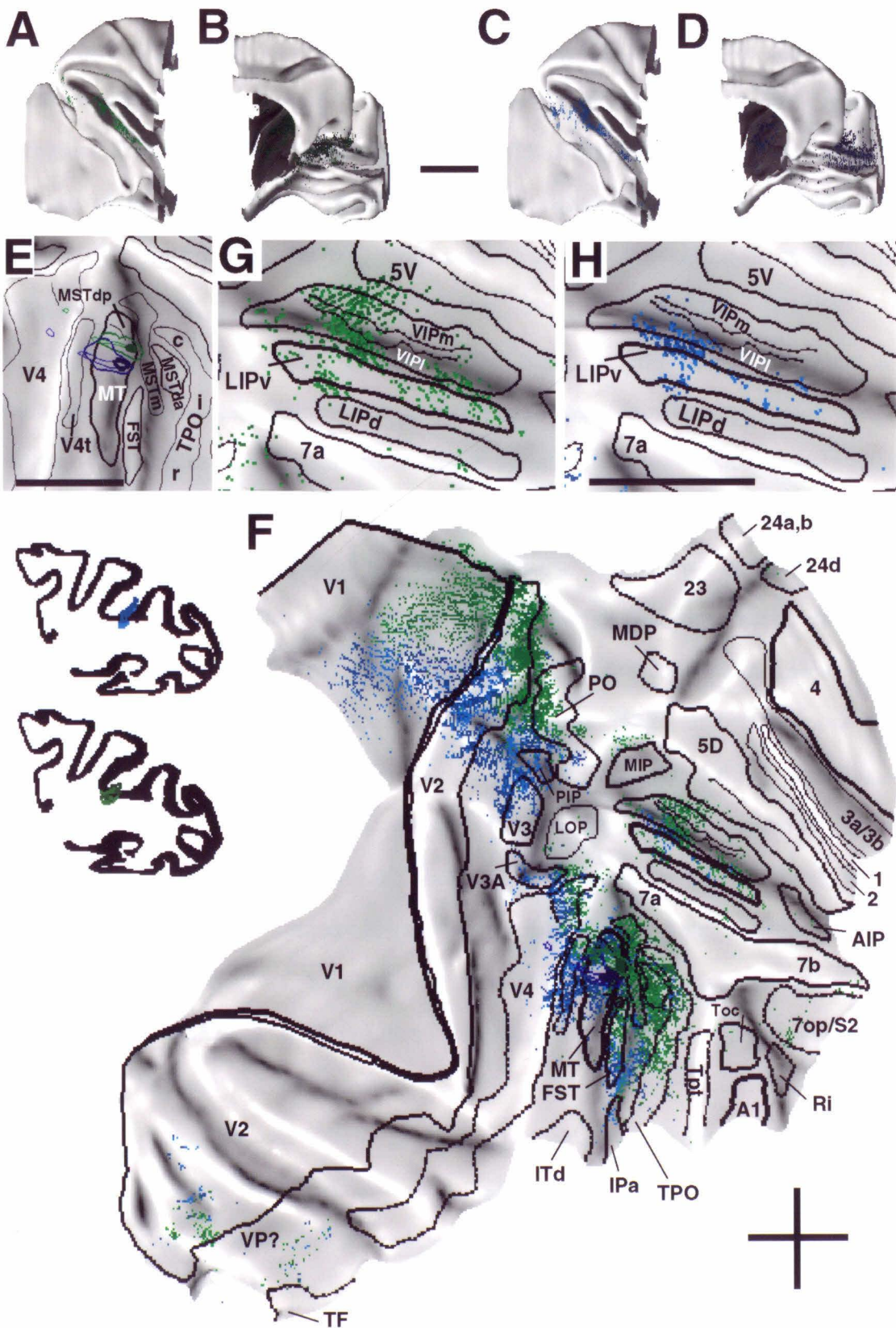
Case D. Area VIP was originally defined on the basis of its connections with MT (Maunsell and Van Essen, 1983), and we examined this pathway in greater detail in relation to architectonic subdivisions of the IPS. As illustrated in Figure 9, case D included a FB injection restricted to the posterior portions of MT (peripheral visual field representation), including all layers, and a closely spaced DY injection that included all layers of MT and probably

portions of MSTdp. The approach for both injections was through the cortex of area V4 and V4t.

The global pattern of connections from both MT injections in case D was consistent with previous studies (Van Essen et al., 1980; Ungerleider and Desimone, 1986b). Labeled fields were present in several visual areas in the occipital and parieto-occipital region, in the superior temporal sulcus, and in the IPS. Label in topographically organized visual areas was predominantly located in the lower peripheral visual field representations. Strong topographically organized projections from layer 4B of V1 confirmed that both injections included area MT (Ungerleider and Desimone, 1986a). Strong separated labeled fields were present in dorsal V2, and lighter in ventral V2 and in the vicinity of VP (upper visual field). Moderate FB label was present in V3 and lateral portions of PO, both representing the lower visual field, while DY label was relatively stronger in medial portions of PO (upper visual field). This discrepancy may be due to DY uptake in MSTdp (see below).

Figure 9 (panels G and H) shows an expanded view of the IPS, illustrating the distributions of DY and FB labeled cells separately. Label from both tracers was concentrated near the fundus of the IPS, including areas LIPv, VIPl, and VIPm. In LIPv, DY and FB labeled cells were intermixed and distributed throughout the area. A heavy DY patch was present in the posterior half of VIPm, and a strong FB labeled field was present centered in the transition zone of LIPv and VIPl. The DY injection most likely included portions of MSTdp (injection compromised the histology), which may account for the relatively stronger DY label in area VIPm, in addition to DY label (but no FB label) in areas 7op, 7b, Toc, 24d, medial PO, and cortex posterior and dorsal to MIP. This latter region (posterior to MIP) may correspond to V6A of Galletti et al., (1996b), which is a region involved in visually guided reaching.

Figure 9. Case D (94EL) illustrating the distribution of label following an injection of FB into posterior portions of MT, and DY injection centered in MT encroaching on MSTdp. (A-D) 3D views of reconstruction. The cortical block was cut orthogonal to the IPS. Middle left inserts show coronal sections containing the DY and FB injection cores. (E) Flat map showing injection sites. The architectonic border at the MT/MSTdp transition was compromised by the DY injection. (F) Flat map showing the distribution of FB (11,230 cells) and DY (15,047 cells) cell label. Map includes 46 areas and zones. (G, H) Expanded view of the IPS showing DY and FB labeled cells, respectively. Scales are 1 map-cm. Other conventions as in Figure 1.



Case E. The results from case E largely support those of cases A, B, and C, but include injections located in different portions of areas LIPv and VIPl and 7a/7b, consequently showing some variation in the distribution and relative strengths of inputs. Case E included a large FB injection of LIPv and VIPl, a medium sized DY injection in the VIP/AIP transition region (most likely VIP), and an AG injection in 7a/7b. Figure 10 illustrates the injections and resulting patterns of label.

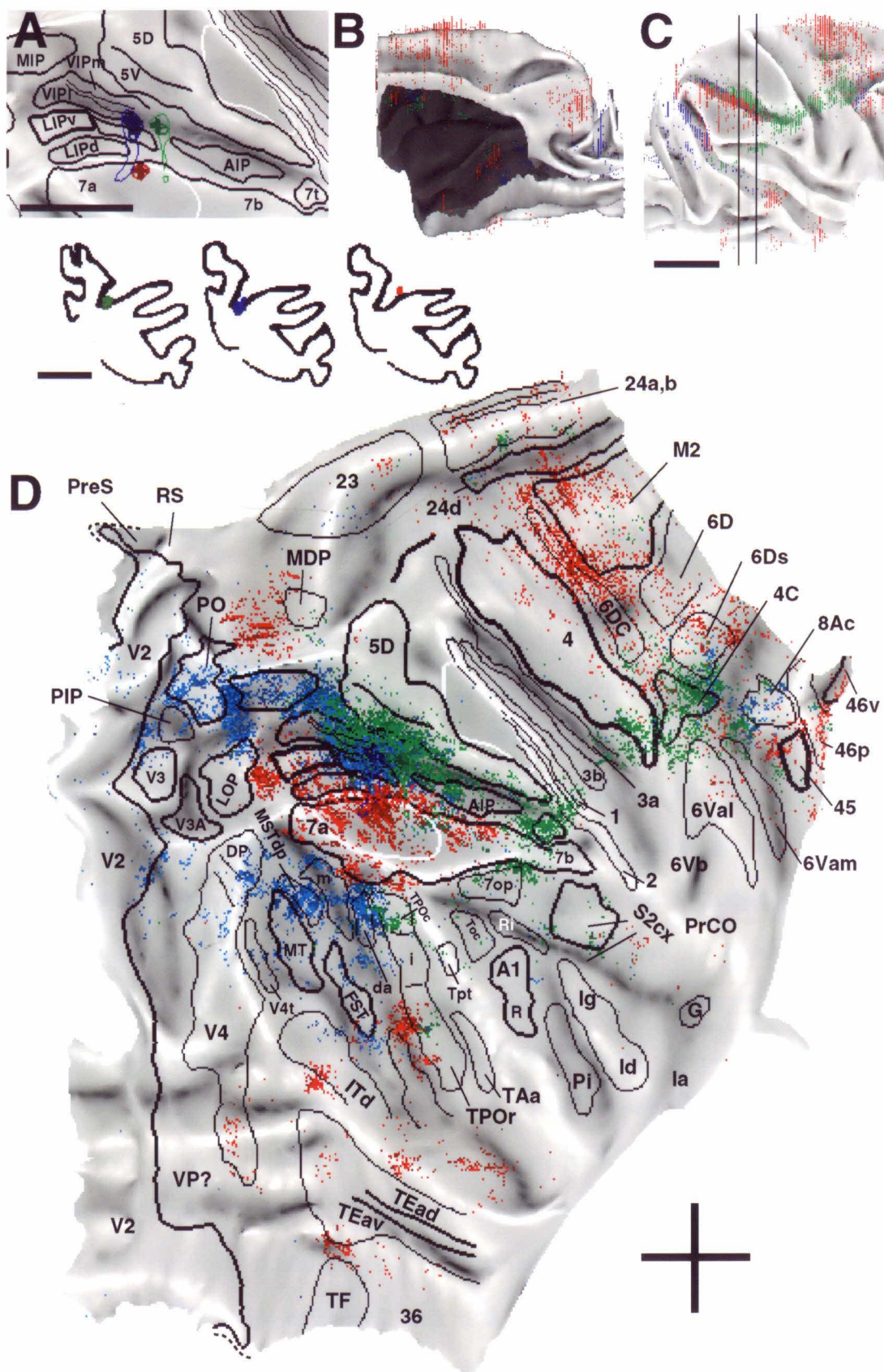
The FB injection resulted in heavy label from the IPS and POS region, moderate to dense label from the posterior STS and from the posterior arcuate region, in addition to sparser connections from the lateral sulcus and cingulate cortex. Relative to architectonic regions, the connections included areas similar to those projecting to VIPl and LIPv in previous cases (Figs. 1 and 8). Outside the injection region, the heaviest projections originated from the MT/MSTdp region and MSTda, areas 8Ac and 6Ds, and the MIP/PO region. The distribution of label resulting from the FB injection (LIPv and VIPl) was consistent with connections supporting a role in visually guided reaching, especially including the label in dorsal (6Ds) versus ventral premotor cortex (Tanné et al., 1996). Significant label in topographically organized visual areas predominantly included lower peripheral visual field representations, including V2, V3, PO, V4, and MT. In sensorimotor cortex, light label was present in the estimated arm and hand representations of 24d, 4, 3a, 4C, 1/2. Label in 7b, S2 and M2 was sparse.

The DY injection was likely to have been centered within VIP, though the architectonic borders were compromised by tissue damage, and thus placed in a transition region between VIP and AIP. The resulting pattern of label was similar to that shown for the DY (VIPm) injection of case B (Fig. 4). The heaviest projections originated from polymodal and sensorimotor-related

cortex, including the much of the IPS, and cortex extending from the posterior arcuate to the central sulcus. Moderate to light label was present in posterior portions of the STS, lateral sulcus, and cingulate cortex. Connections with somatotopically organized areas were in the vicinity the arm and hand representation of 24d, 4, 3a, 1, and 2, and of the hand/arm and possibly face representation of 4C, M2 and the S2 complex. Inputs from visual-related cortex included moderate projections from MSTda, and light projections from MT, MSTdp, MSTm, LOP, MIP, MDP, LIPd, and LIPv. Projections from the tip of the IPS (zone 7t) were particularly prominent in this case, supporting area VIP involvement in a vestibular network (Graf et al., 1996; Büttner and Büttner, 1978; Akbarian et al., 1994). Light label was also present in the caudal temporal-parietal region (areas Tpt, Toc, and TPOc) which is a region that is responsive to the location of auditory stimuli (Leinonen et al., 1980). As a side note, DY label within TPOc appeared to fall largely within the dense patches of SMI-32-ir cell label, which is similar to projections from frontal cortex as described by Cusick et al., (1995).

In Figure 10, AG label from the 7a/7b injection included heavy label along the lateral bank of the IPS and parietal lobule, and dense label in frontal (premotor) cortex. Moderate label was also present in anterior portions of the STS and temporal cortex, and in cingulate cortex. In contrast with the other injections presented thus far, strong projections originated from estimated leg and trunk representations of premotor cortex, including areas 6DC and M2, and area 4. This pattern is also in contrast with connections observed in some studies (cf. Cavada and Goldman-Rakic, 1989b). Other sensorimotor projections originated from 24a, 24b, 24d, 23, 6D, 6Ds, 4C, 6Val, and possibly the S2 complex. A notably distinct labeled field was present ventral to MDP, in contrast with MDP projections to VIP (DY injection) shown in this and previous cases (i.e.

Figure 10. Illustration of the three injections of case E (94IR). (A, B) Tracer injection sites in flat map and coronal section representation. The FB injection of LIPv/VIPl was approached through the cortex of 7a and LIPd, and included layers of VIPl and supergranular layers of LIPv. The DY injection of presumed VIP was through 7a/7b and the LIP/AIP transition region, and included layers 1 through 4. The track damage of FB and DY injections encompass the injection halos in this case. The AG injection included layers 1 through 4 of 7a/7b. (C, D) 3D views of reconstruction showing label of all three injections (above layer 4 surface). (E) Flat map showing the cell label distribution of FB (14,993 cells), DY (13,392 cells), and AG (10,838 cells). Map includes 66 areas and zones. Portions of area 5 and 7a/7b were compromised by tissue damage (white outlines), and a cortical dimple in the parietal lobe is evident in the curvature map (resulting from the skull opening). Scales are 1 map-cm. Other conventions as in Figure 1.

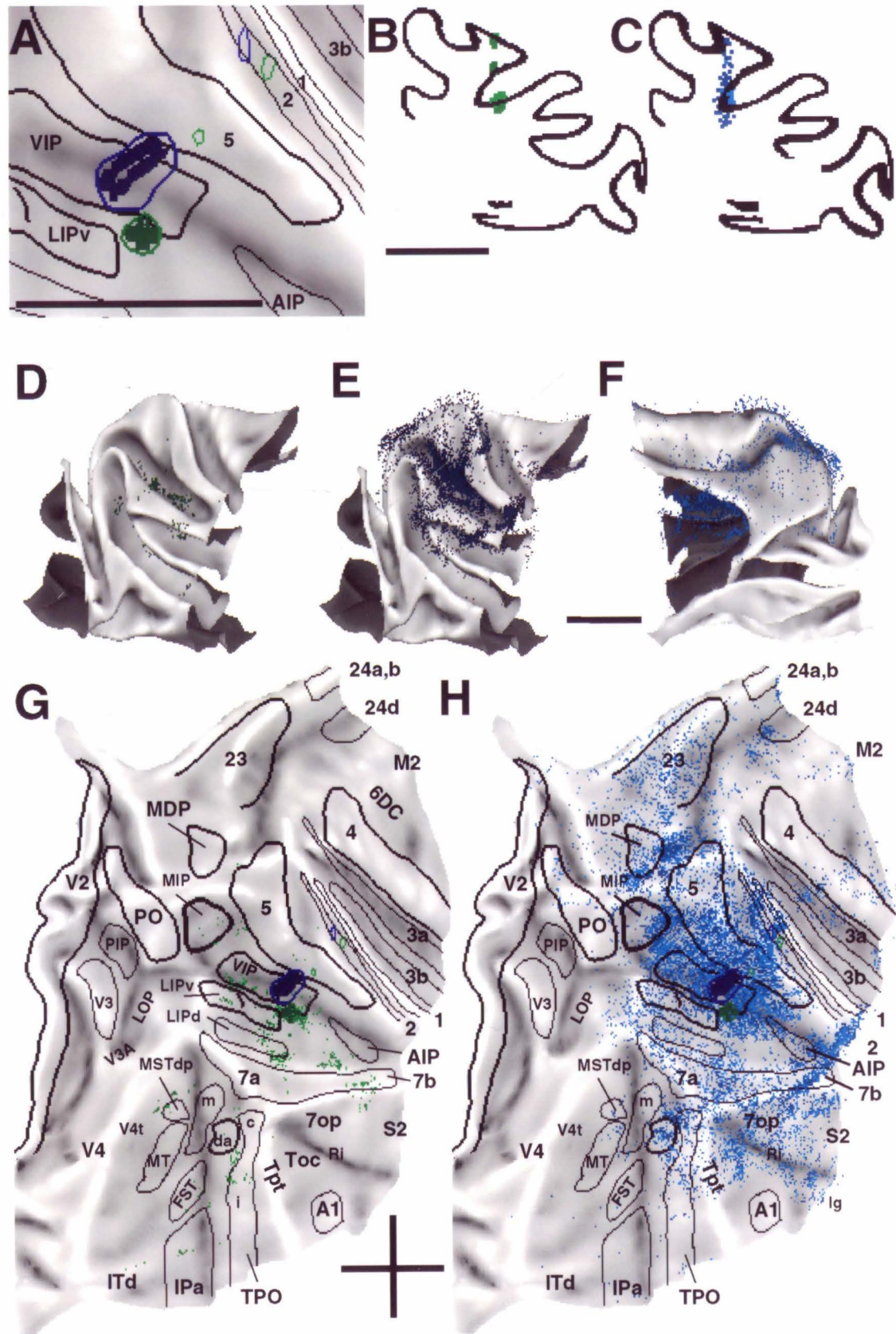


Figs. 1 and 4). Label in the STS and temporal lobe was patchy. As with the DY label in case C (Fig. 8), AG label in the STS included two patches within and near ITd, separated by roughly one centimeter, suggesting the presence of separate areas. Also, a dense patch of label is present in the vicinity of TPOr. Projections from early visual areas were relatively light.

Overlap of the three tracers outside the injection region was light to moderate overall. In frontal cortex, all three tracers were present (light to moderate) in somatomotor and oculomotor cortex, including portions of area 24, 6Ds, 4C, and 8Ac. In the IPS, posterior portions of LIPd, LIPv, VIP, and MIP also contained light to sparse label from all three tracers. In the STS, separate yet juxtaposed DY, AG, and FB labeled fields span the region near the confluence of TPOr, IPa, and FST, and also the 7a, 7b, TPOc, and MSTda region.

Case F. As Illustrated in Figure 11, case F included two tracer injections, a large FB injection including all layers of VIPl and VIPm, and portions of area 5V, and a small injection restricted to superficial layers near the anterior tip of LIPv and VIP. The FB injection resulted in a distribution of label similar to that shown for the VIPm injection of case B (Fig. 4), but included a wider range of inputs from somatosensory related cortex, which is presumably due to tracer uptake in 5V. As with the VIPm injection of case B, FB cell label in Figure 11 was moderate to strong in MDP, MIP, anterior 7b (and 7t), MSTda/TPOc, and in posterior arcuate areas (not shown), which is characteristic of VIP injections. Visual connections were light to moderate, and included dorsal V2, PO, MIP, MDP, 7a, possibly DP, MSTdp/MT, IPa, MSTda and TPOc. The distribution of label in premotor cortex was similar to other VIP injections, including the estimated arm and hand representations of 24d, 4, 3a, 1, and 2. Though not included in the unfolded block in Figure 11, moderate to

Figure 11. Illustration of DY and FB injections of case F (93GR), and distribution of label. (A) Flat map showing injection sites. The approach for the FB tracer was through area 2, white matter, and zone 5V. The FB injection included all layers of VIP (VIPl and VIPm) and deep layers of 5V. The approach for the DY tracer was through area 2, white matter, 5V, then crossed the lumen of the IPS and into the lateral bank near VIPl and LIPv. The DY injection included layers 1 through 4 of cortex. (B, C) Sections containing the DY and FB injection core (tracks as well as core and halo are depicted). Sections were cut perpendicular to the IPS. (D-F) Distribution of DY and FB label on the three-dimensional layer 4 surface reconstruction. V1 was removed from the reconstruction. (G, H) Flat maps displaying the resulting pattern of retrogradely labeled cells from the DY (1,014 cells) and FB (18,082 cells) injections, respectively. Subdivisions of VIP were not evident in this case, due to compromised histology. Scales are 1 map-cm. Other conventions as in Figure 1.



strong projections also originated from the estimated hand and arm (and possibly face) representation of the S2 complex, M2, and 4C (also see Table 4).

Unlike other VIP injections, the FB injection of case F produced relatively stronger label in several somatosensory areas, including 23, 5, 7a, medial portions of 3a, 1, and 2, and the S2 complex, consistent with extension of the injection site into area 5 (Jones et al., 1978; Pandya and Seltzer, 1982).

Projections from the auditory-related cortex (Tpt, Toc, and TPOc) were notably stronger than in other cases, though it is not clear whether these projections are to 5V or VIP. Note that FB label forms a relatively sharp transition along the ventral bank of the lateral sulcus, near the border of A1 (cf. Morel et al., 1993). Other architectonic boundaries that are respected by FB labeled fields include areas 23, PO, and MSTda, and the posterior border of VIP.

The DY injection was located outside the core outline of VIP immediately anterior to LIPv, and resulted in label in both visual and somatosensory areas. Visual-related inputs originated from LIPv, LIPd, MSTdp, MSTda, IPa, and possibly TPOc/TPOi, FST, and MIP. Label in the frontal block (not shown) included areas 8Ac, and portions of area 46 (refer to Table 4). Somatosensory inputs were relatively strong from 7b and the surrounding cortex. The pattern of label from this injection was more similar to VIP than LIPv injections. Regardless of the semantics, this region of cortex is likely to be involved with integrating visual and somatosensory information.

Summary of cortical connections

Table 4 summarizes the connections of 20 separate cortical injections of the IPS and STS from 11 animals. This table is arranged to illustrate the consistency of projections to certain areas or zones, and to examine trends in

label across injections that included more than one architectonic core region. Each column represents one injection, including the 15 injections previously illustrated. The columns are arranged in a geographic sequence, with columns on the left showing injections of anterior portions of the IPS (2 cases, somatosensory-dominated cortex), and a progression to injections along mid- portions of the fundus of the IPS involving VIPl or VIPm (7 injections), injections of the lateral IPS and parietal lobule (2 including LIPv, 3 including 7a/7b), and on the right showing injections within the STS (4 injections including MT or MSTdp). The rows include 63 architectonically distinct areas, zones or combined areas, and are arranged in 9 groups: dorsal and ventral occipital visual cortical regions; areas of the STS; visual-related parietal cortex; somatosensory areas; areas of the lateral sulcus; motor plus dorsal premotor areas; ventral premotor areas; cingulate cortex; and prefrontal cortex.

The injection site(s) are depicted in each row by black entries, with the estimated effective uptake strength indicated, ranging from strong (+++) to light (+). The remaining white to dark gray shaded entries encode the strength of each projection relative to the particular tracer injection size, ranging from absent (-) to strong (+++). These are intended to give an indication of the relative size and location of a projection and are only semi-quantitative. A projection was considered "strong" if the densest region of labeling within a core region had more than about 20 cells per mm^2 (typically saturating a portion of an area or zone on the flat maps, such as the DY label in area MIP from Figure 1G and 2B). Moderate projections contained fewer than 20 cells per mm^2 , and typically contained several dozen cells (such as the DY label in MDP of Fig. 1). Light projections either had more than 10 cells within a core region or had at least one small patch of labeled cells with a density

Table 4. Summary of projections to 20 injections of parietal cortex and the STS, indicating relative strengths (refer to text). Injections restricted to one architectonic zone are indicated by densely bordered columns. Size of injections from Table 1: S, small; M, medium; L, large. Vm, VIPm; Vl, VIPl; Lv, LIPv; Ld, LIPd; a= anterior portion of area. *Case 94I-AG contained a strong labeled field ventral to MDP not indicated (see Fig 10). Note that some rows include two or more areas or zones, and some areas and zones depicted in the flat maps were excluded from this table. The question marks in the black boxes indicate that the injection site was outside the core outline of the area(s) indicated.

Table 4. Summary of Data

	SS/M		IPS Fundus								Lateral IPS						STS				
Case	B	H	F	E	B	K	A	E	G	C	A	F	C	E	A	B	D	D	I	J	
Tracer	FB	DY	FB	DY	DY	FB	DY	FB	FB	FB	FB	DY	DY	AG*	AG	AG	DY	FB	DY	DY	
Size	M	M	L	M	M	L	L	M	L	M	S	S	L	M	M	L	M	M	S	S	
Inj. site	AIP	AIP	VIPm	VIP	VIPm	VIPi	VIPi	VIPi	VIPi	LIPv	LIPv	VIPi	LIPd	7ab	7b	MSTdp	MT	MT	MT	MT	
Inj. site	7b?	7b?	5V:Vl	AIP		LIPv	Lv	LIPv	LIPv	VIPi		LIPv				?	MSTdp				
AREA/																					
V1	-	-	-	-	-	-	-	-	?	?		-	-	-	-	-	+++	+++			
V2d	-	-	?	-	-	+	+	+	+	+	++	?	-	-	-	-	++	+++	+++		
V3	-	-	-	-	-	+	-	+	+	++	++		-	-	-	-	+++	+	+++	++	
V3A	-	-	-	-	?	+	-	-	?	?	++	-	-	-	-	-	+++	+	+++	+	
LOP	-	-	+	?	+	++	++	+	+	++	+	-	?	?	-	-	?	?	-	?	
PIP	-	-	-	-	?	+	++	+	++	++	++	-	-	-	-	-	++	++	++	?	
PO	-	-	+	-	++	++	++	++	++	++	++	-	?	-	-	-	+++	++	+	++	
DP	-	-	?	-	-	-	-	-	+	?	+	-	-	-	-	-	++	+++	+	?	
V4d	-	-	-	-	-	-	+	+	?	+	+	-	++	-	-	-	++	+	+	+	
V4v/VOT	-	-	-	-	-	-	-	-	-	?	-	-	+	+	?	-	+	?		?	
V2v	-	-	-	-	-	-	-	-	-	++	?	-	-	-	-	-	++	+	+	+	
VP region	-	-	-	-	+	-	+	-	?	?	-	-	-	?	-	-	+++	+	+	++	
TF/TH	-	-	-	-	-	-	-	-	?	-	-	-	-	?	-	-	++				
TEad/TEav	-	-	-	-	-	-	-	-	-	-	-	-	+	+	?	-	?			-	
V4tp	-	-	-	-	-	+	-	+	?	++	+	-	+	-	-	-	?	++	+++	+	
V4ta	-	-	-	-	-	?	+	?	?	+	+	-	++	-	-	-	+	-	?	+	
MT	-	-	+	?	-	++	+	++	++	++	+++	++	?	-	-	-	++	+++	+++	+++	
MSTdp	-	-	+	+	?	++	++	+++	++	+++	++	++	+	-	-	-	+++	+	+++	++	
MSTm	-	-	?	+	+	++	+	++	++	++	?	?	+	?	-	-	+++	+++	++	++	
MSTda	?	?	+++	+	++	++	++	+++	++	++	+	+++	?	-	-	-	+++	+++	+	++	
TPOc	-	-	++	++	++	?	+	+	++	+	+	+	+++	-	++	-	+	++	+	-	
TPOi	-	-	+	?	+	?	++	+	+	+	?	?	+	?	-	+	+	+	?	-	
TPOr	-	-	+	+	?	?	+	-	++	-	-	-	++	+	?	-	+	?	?	-	
FST	-	-	?	?	+	++	+	+	++	++	+	+	++	?	?	-	+++	++	++	++	
IPa	-	?	+	-	-	+	+	?	+	+	-	+	++	?	+	-	+	?	+	+	
ITd	-	-	-	-	-	-	+	?	+	-	-	?	+++	++	+	-	-			-	
MDP	-	-	+++	+	+++	+	?	++	?	+	+	-	+	+	++	-	?	?	-	-	
MIP	+	?	+++	+	++	+++	+++	++	++	+	++	+	?	+	?	-	?	?	-	+	
7a	-	-	+	-	-	-	+	?	+	+	?	-	++	++	+	-	-	?	-	-	
LIPd	-	+	+	+	++	+	++	+	+	++	+	++	++	++	+	-	+	-	-	-	
LIPv	-	+	++	+	+++	+	+	++	+++	+++	++	?	+++	++	+	-	+++	++	++	++	
VIPi	-	-	++	+	+++	+++	+++	+++	+++	+++	++	?	+	+	+	-	++	++	++	++	
VIPm	+	+	+++	+++	+++	+	+++	+++	+++	+++	+	?	+	-	++	-	++	++	?	?	
5V	+++	+++	++	+++	++	+	+++	+	++	-	?	?	+	-	-	-	-	?	-	-	
AIP	++	++	++	++	+	?	+	?	+	-	+	?	+	-	?	-	-	-	-	-	
7t	+++	+++	+++	+++	+	?	++	-	?	-	+	-	?	-	+	-	-	-	-	-	
7b	?	?	++	+	+++	-	++	+	++	-	?	+++	++	++	++	-	?	+	-	-	
7op	+	+	++	++	+	-	+	?	?	-	-	?	++	-	++	-	?	+	-	-	
area 3a	-	+	++	++	-	?	+	?	+	-	-	-	-	-	-	-	-	-	-	-	
area 1	?	+	++	+	?	?	+	-	+	-	-	-	-	-	-	-	-	-	-	-	
area 2	+	+	++	+	?	?	+	?	+	-	-	-	-	-	+	-	-	-	-	-	
5D	++	+++	+++	+	+	?	++	?	?	-	-	-	-	-	?	-	-	-	-	-	
S2 cmpx	+++	+++	++	++	+	-	++	+	+	-	-	-	++	+	+++	-	-			-	
Ri	+	?	++	-	-	-	?	?	?	-	-	-	-	-	?	-	?	-	-	-	
Ig/Id	+	+	+	-	?	?	+	-	?	-	-	-	+	-	++	-	-			-	
Tpt	-	-	++	+	?	-	?	?	-	-	-	-	-	-	-	-	-	?	-	-	
Toc	+	?	++	+	+	-	-	?	?	-	-	-	?	?	?	-	-	?	-	-	
area 4	-	+++	+++	++	-	+	++	+	++	-	-	-	-	+	-	-	-	-	-	-	
4C	+		+++	+++	++	++	++	++	++	+	?	-	+	+	++	-	?				
6Ds	+		+	?	++	-	-	?	?	+	-	-	++	++	?	-	?				
M2 (SMA)	-		++	+	++	+	+	?	++	+	-	-	+	+++	+	-	+				
6Val	++		+	-	+	-	+	-	-	-	-	-	+	+	+	-	-				
6Vb/PrCO	-		-	-	-	-	-	-	-	-	-	-	-	-	+	-	-				
24d	-	+	++	+	+	?	+	+	?	-	-	-	-	+	-	-	-				
24a/b	+		+	+	+	?	+	?	+	+	-	-	++	++	++	-	+				
23/30/29	?	?	++	-	?	-	-	+	+	?	-	-	+	+	-	-	-	-	-	-	
8As	-		?	+	-	+	-	-	?	+	-	-	+	?	-	-	+				
8Am	-		+	?	+	?	-	-	+	?	-	-	+	?	-	-	-				
8Ac	-		++	++	++	++	++	++	++	++	++	++	+	+	?	-	++				

greater than 2 cells per mm^2 . A lower density of label within a core region was designated as questionable ('?'). In some instances, a significant labeled field straddled a border outline (+?), indicating that the projection zone may have a stronger assignment than that based just on the core region. In general, Table 4 provides a lower bound for the connectivity associated with a given injection, taking into account the sampling of sections, exclusion of some label lying outside core outlines, and exclusion of regions not analyzed due to compromised tissue in some cases. On the other hand, most injection sites involved more than one area or zone, and are thus likely to overestimate the contributions of a single area or zone.

Connections of VIP. The significant connections of VIP (VIPm plus VIPl) included 27 architectonically distinct areas and zones, spanning several functional divisions. The global pattern of connections is also represented in Figure 12. The strongest connections included visual areas MSTda, LIPv, and 8Ac (visuomotor), the somatosensory zone 5V, bimodal areas MIP and MDP, and premotor area 4C. Moderate projections to VIP covered a similar range of modalities, including visual inputs from PO, LOP, PIP, LIPd, FST, and MSTm, somatosensory inputs from AIP, 7op, and the S2 complex, inputs from polymodal TPOc and 7b, and motor/premotor inputs from area 4 and M2. Light (but consistent) projections originated from area 2, Toc, TPOi, 24d, 24a/b, 6Vam, and area 46 subdivisions. An additional 11 areas and zones projected to different portions or patches of VIP in varying strengths (light to strong), including MT, MSTdp, V2, 7t, TPOr, IPa, 5D, 6Ds, 6Val, area 1, and area 3a. In several cases, light projections originated from TPOr and surrounding cortex, which is a region that contains visual and somatosensory responsive bimodal cells as does VIP (Mistlin and Perrett, 1990).

The four architectonic borders of VIP with surrounding areas LIPv, PIP, 5V, and AIP correlated with changes in density of connections in many examples. The location of the VIPm/5V architectonic transition zone correlated with labeled field resulting from injections of several visual-related areas, including MT (Fig. 7), MSTdp (Fig. 4), LIPv (Figs. 2, 6), 7b/7a (Fig. 2), and 7a (Fig. 94IR), which all showed moderate to strong label in VIPm, gradually or sharply diminished in the VIPm/5V transition region, and little to no label in 5V. The location of this border in some cases was further dorsal than the location described based on physiological grounds (Colby et al., 1993a: Fig. 1; also see Chapter 2). These differences in location might be attributable to species differences (*M. fascicularis* versus *M. mulatta*) and/or animal variability. Support for the distinction between VIPl and LIPv included differences in labeled field strengths resulting from injections of MSTdp (95D-AG, Fig. 6), some MT injections (Table 4), and of injections of VIP itself (cf. 93G-FB, Fig. 10). These results are consistent with the LIPv/VIP boundary described by Blatt et al., (1990) and Colby et al., (1993a,b). The PIP/VIP border, though subtle in architecture, was supported by connectivity patterns with MT and MSTdp, wherein PIP and VIP contained separated labeled fields. Additionally, injections of anterior portions of VIP (Fig. 9, 93G-FB) and 7b (Fig. 2, 94C-AG) resulted in label throughout much of VIP, but not in PIP. The AIP/VIP boundary was best supported by connections with visual-related areas including all five injections of the STS (MT and MSTdp), plus LIPd/7a and LIPv.

Previous studies have identified a number of areas having connections to or from the vicinity of VIP, i.e. in the fundus of the IPS near its middle third. From visual-related cortex, the estimated location of VIP is connected with areas V2 and possibly V4 (Seltzer and Pandya, 1980), V3 and VP (Felleman et al.,

1997), PO (Seltzer and Pandya, 1980; Colby et al., 1988), MT (Van Essen et al., 1980; Ungerleider and Desimone, 1986b), MSTda (DMZ), MSTm, and possibly FST (Boussaoud et al., 1990), LIPd and LIPv (Blatt et al., 1990; others), MDP (7m) and 7a (Pandya and Seltzer, 1982; Seltzer and Pandya, 1986), and polysensory TPOc (TPO-4, Seltzer and Pandya, 1991). From sensorimotor related cortex, connections with the estimated location of VIP included areas 1 and 2 (area 1 hand representation, Burton and Fabri, 1995; arm representation of 1 and 2, Pearson and Powell, 1985; Seltzer and Pandya, 1980), 7t (Pandya and Seltzer, 1982), 5V and 7b (Seltzer and Pandya, 1986), area 4 (Künzle, 1978; Leichnetz, 1986), and premotor areas 6Val and 4C (cf. Godschalk et al., 1984). Many of the above studies also used retrograde tracing techniques, indicating that most of the cortical connections of VIP we observed are reciprocal. Overall, the connections of VIP were largely consistent with previous connection studies, though the relative strengths and distributions were heretofore unknown.

The connections of the architectonic subdivisions VIPm and VIPl differed in the relative strengths of connections: VIPm connections were stronger with MDP, M2 and possibly 7b, 7op, and Toc, while VIPl connections were stronger with visual areas V2, PIP, MT, and possibly LOP, V4t, LIPv. These differences suggest relatively stronger visual input to VIPl, and stronger sensorimotor input into VIPm. Other differences in connections with VIP were evident along the antero-posterior extent of the fundus within VIP, suggesting stronger sensorimotor connections with anterior portions of VIP.

The visual connections of VIP (especially VIPl) were similar overall to the distribution of connections of LIPv, with the exception that projections from areas V3, PIP, V4t, and possibly V3A were stronger and more consistent for injections involving LIPv. Additionally, our data suggest that V2 projections to the IPS are concentrated near the VIPl/LIPv transition region, and include

the lower, and to a lesser extent the upper, peripheral visual field representations of V2. In contrast with LIPv, the connections of VIP (VIPl and VIPm) were markedly different in that the latter included heavy label from numerous somatosensory, motor and polymodal areas, as mentioned previously. Overall, these data suggest that architectonically defined VIP of this study is not homogeneous in its patterns of connections, but it remains unclear whether the differences reflect distinct medial and lateral subdivisions, a gradient in connectivity, or some other type of modular organization.

Area MT projects to both to LIPv and VIP, though connections were generally stronger with LIPv. This bias is puzzling, given that direction selectivity is prominent in MT and VIP, but not in LIPv (Colby et al., 1993a,b).

Connections of LIPv. The connections of LIPv with the remaining portions of the hemisphere were largely consistent with the results reported by Blatt et al., (1990), though we found some differences relating in part to differences in the partitioning schemes. To the list of known LIPv connections, we can add FST, TPOc, LOP, and 6Vam (thought to be part of the frontal eye fields). In some cases, additional light to moderate connections with LIPv included V2, TPOi, M2, 24b, and 4C, but the consistency of these pathways awaits further verification. The inputs to LIPv from visuotopically organized areas were predominantly from peripheral representations of the visual field, with a bias towards lower visual field inputs (compare top two clusters of rows). This bias may relate to the location of the injections within LIPv (which tended to be in ventral portions) rather than the area as a whole.

Connections of the STS. The connections of MT depicted in Table 4 are consistent with previous studies (Van Essen et al., 1980; Ungerleider and Desimone, 1986b), and also include light projections originating from IPa. MT projections from VIPl and LIPv were stronger than those from VIPm, consistent with the results from IPS injections already noted. Connections between MT and areas VIP and LIPv did not show an orderly topographic organization (i.e., Fig. 9), though there was some patchiness consistent with possible coarse and irregular topography (cf. Blatt et al., 1990).

The connections of MSTdp overlapped many of the areas connected with MT, with the major exception of no connections with V1. Additionally, MSTdp was more heavily connected with VIPm, and unlike MT received light inputs from TPOc, TPOi, Toc, 24d, and 7op/7b (based on two cases). The other connections of MSTdp in case 95D-AG may have resulted from tracer uptake into TPOc as mentioned previously, and thus should await further verification.

Connections of AIP. The connections of AIP, though derived from injections that were not restricted to the core region, included the sensorimotor regions 5V, 5D, 7b, 7t, and the S2 complex (see Fig. 13). Light to moderate connections originated from anterior portions of LIPd and LIPv, from VIPm, area 2, insular cortex (Ig/Id), 6Val, 4C and possibly from Ri, Toc, 24a/b, 24d, 46v, 6Ds, 4, 1, 3a, and MIP. Visual areas were largely devoid of label, except for neighboring areas LIPd, LIPv, VIPl, VIPm, and possibly areas MIP and 46.

Hierarchical relationship of VIP. On the basis of the laminar patterns of connections, our results support the hierarchical placement of several visual and somatosensory areas with respect to the placement of VIP

(VIPl plus VIPm) as described by Van Essen et al., (1990). Several visual and somatosensory areas showed a feed-forward pattern of projections to VIP across multiple cases included areas V2, PIP, MT, and possibly V4, plus areas 1 and 2. Similarly, feed-back projections to VIP originated from 24, M2 (SMA), and possibly some other regions of premotor cortex. At odds with the hierarchical scheme by the above authors, the S2 complex (both ipsilateral and contralateral) consistently showed a strong feed-back pattern of connections, suggesting that it be placed higher than VIP.

Figure 12. Schematic summary of VIP connections. Arrow thickness and darker shades of gray correspond to stronger inputs from different functional groups of areas.

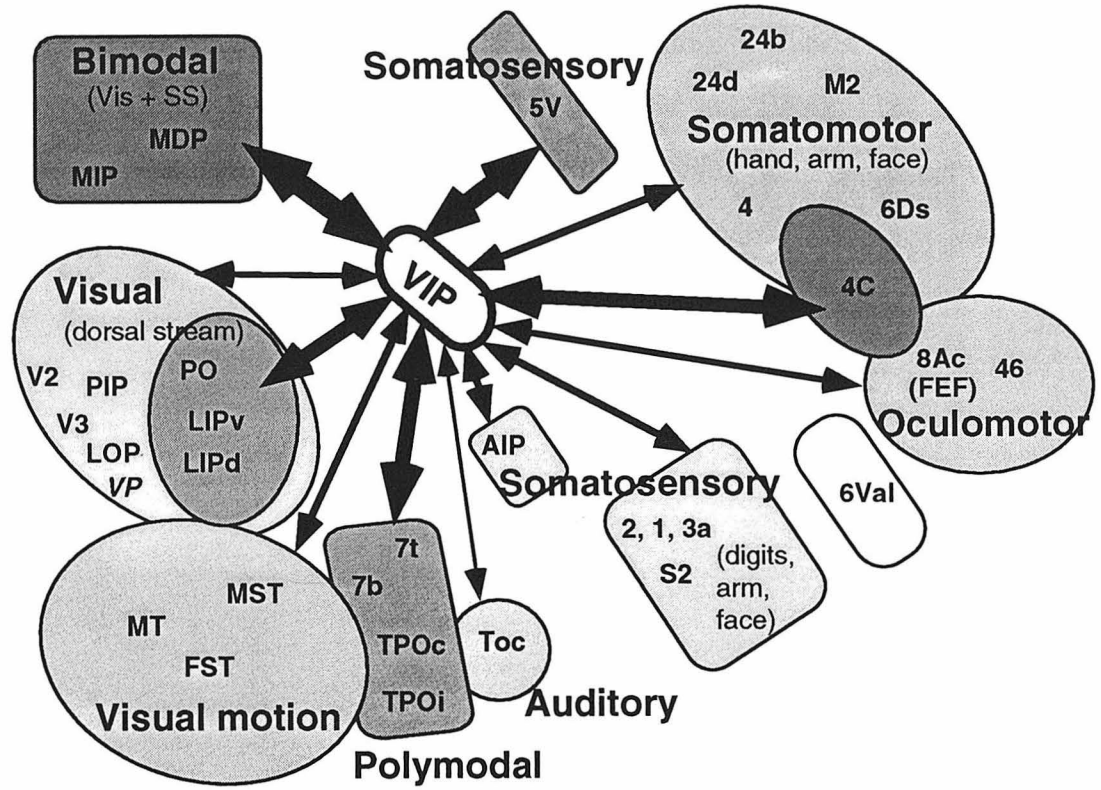
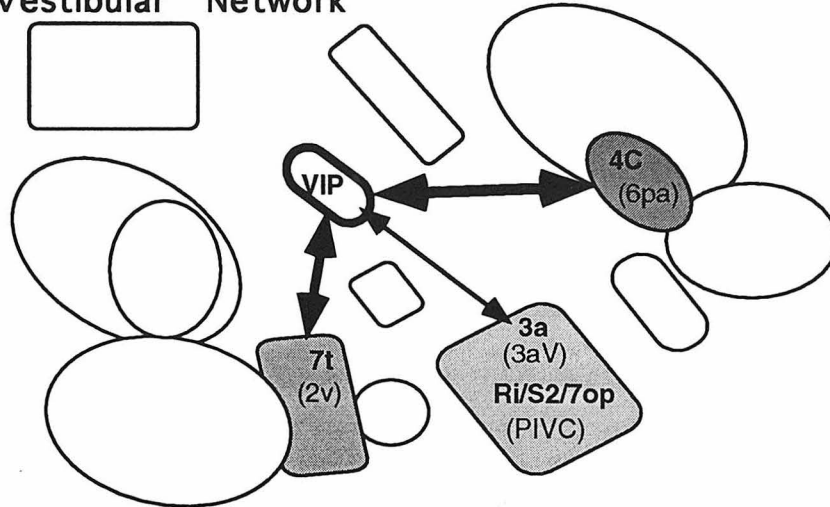
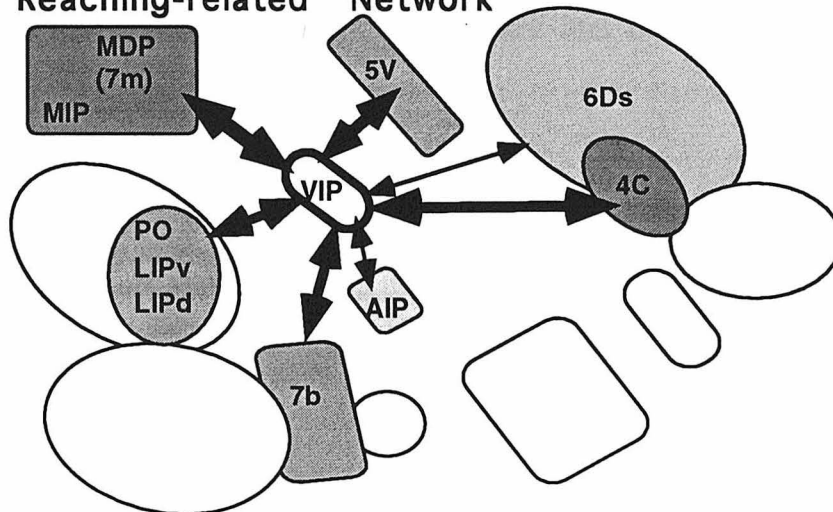


Figure 13. Summary of previously proposed networks and their relation to connections of the IPS. (A) Vestibular network including a subset of cortical areas known to project to vestibular nuclei (Akbarian et al., 1994). (B, C) Grasping versus reaching networks based on connections with premotor cortex (Tanné et al., 1996). See text for details.

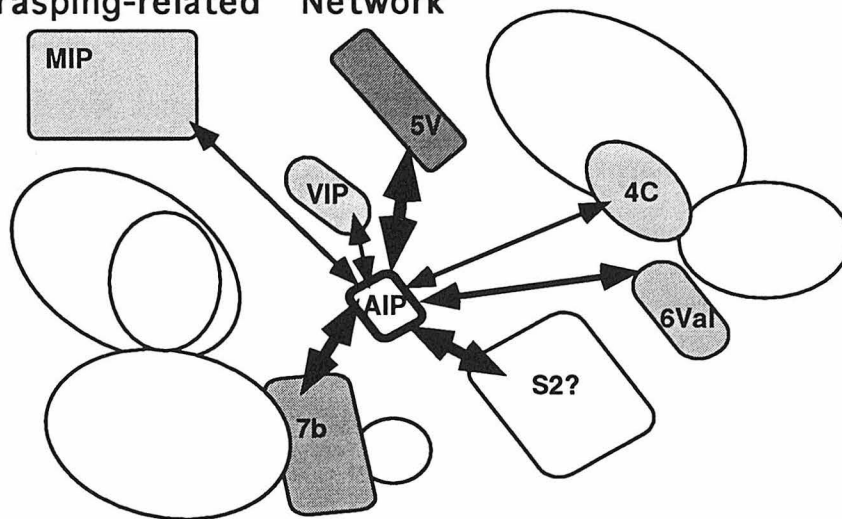
A. Vestibular Network



B. Reaching-related Network



C. Grasping-related Network



DISCUSSION

In this study, we mapped the overall pattern of cortical inputs revealed by tracer injections into a number of architectonically identified regions in parietal cortex, especially within the IPS. By displaying connectivity patterns on cortical flat maps in relation to geographical landmarks as well as architectonic boundaries, each case provides a large amount of detailed data. Some of our findings confirm results of previous studies, but many reveal previously unreported or poorly characterized connections. However, the interpretation of these data is complex in many respects, particularly in relation to the confidence with which various foci of label can be designated as a particular cortico-cortical "connection" (e.g. a distinct pathway, say, from FST to VIP1).

Consistent with a variety of other connectivity studies (parietal, visual, somatosensory, and motor cortex), deep lying regions of the IPS are most heavily connected with other portions of the IPS plus the posterior half of the STS and premotor cortex near the central and arcuate sulci. Among these regions lie numerous distinct architectonically derived areas and zones (Chapter 2), which in many instances showed a correlation with connections, strengthening the notion that they may have distinct functional roles in sensory and motor integration. Additionally, the different patterns of connectivity detailed in this study are relevant to hypotheses about specific networks involved in different aspects of sensory processing and motor control, especially related to the eyes, head, and upper limbs.

Connectivity as a guide to partitioning

For injections centered in neighboring architectonic zones, patterns of connectivity can help to determine whether to regard them as separate areas or subdivisions of a single area. To reach firm conclusions, however, results must be consistent across cases and be dissociated from technical artifacts. The results of this study have bearing on two proposed cortical subdivisions identified based on architecture as described in Chapter 2, including VIPm versus VIPl, and MT versus MSTdp.

Area VIP (VIPl plus VIPm) has major differences in cortical connections compared to neighboring areas 5V, LIPv, AIP, and PIP. To this extent, connectivity patterns support the identification of VIP as a separate area. However, within VIP, internal differences in connections as well as architectonics was evident. The antero-medial half (VIPm) was distinguished (from VIPl) in several cases by its greater density of myelination and SMI-32-ir cell label, though the border was generally characterized by a gradient rather than a sharp transition (Chapter 2). The connections of VIPm and VIPl were similar overall, though there was a trend for VIPl inputs to be stronger with early visual areas (similar to those of LIPv), while VIPm inputs were stronger with some sensorimotor areas. Conversely, the outputs of VIPl and VIPm differed with respect to projections to areas MT, MSTdp, and the 7a/7b complex. These architectonic and anatomical differences are not sufficient to establish VIPl and VIPm as two distinct areas, but nor do they foreclose this possibility. In either case, examination of physiological differences along the medial versus lateral halves of VIP may prove useful for advancing our understanding of the organization and functions of this area.

Another example of differential patterns of connections across subdivisions includes two heavily myelinated regions, area MT and the neighboring zone we termed MSTdp. Both of these regions appear to have been included as one area in some studies and not in others (Chapter 2). Our evidence indicates that MSTdp has substantially different connections from MT, notably lacking projections from V1, and having stronger connections with higher cortical areas, including VIP, TPO, and possibly some sensorimotor-related regions. Together with the architectonic distinction, connectivity differences strengthen the case that the two regions are separate. MSTdp may overlap portions of the V2 projection region described by Ungerleider and Desimone (1986a), located posterior and dorsal to the zone MTp.

The correlation of tracer labeled fields relative to architectonic boundaries supported the validity of several areas in addition to those mentioned above. For example, in some injection cases, including TPOc, MSTda, FST, LIPv, and MIP, most of the core regions contained moderate to strong label that rapidly diminished in the surrounding transition zone. Additionally, some architectonic borders and zones correlated with differential strengths in connections, including PIP, PO, MDP, MSTm, LIPd, 24d and M2. On the other hand, there are numerous examples lacking any correlation between density of labeling and architectonic borders, just as is seen in other studies of cortico-cortical connectivity (e.g., continuous label or shallow gradients of label across an architectonic border, or label stopping abruptly within an architectonically homogenous region). For example, discontinuity in labeled fields are common in somatotopically organized areas (such as area 1 and 3a connections, Burton and Fabri, 1995), and retinotopically organized areas (i.e.,

upper versus lower visual field representations). Thus, the lack of a tight correlation does not constitute invalidation a given areal boundary.

Areal connectivity patterns

We have identified a number of new pathways and/or have further characterized ones that were poorly understood. The results are derived in part from injections restricted to one area (connected on average with 20 architectonically distinct areas and zones), and injections involving more than one area (averaging 28 connected areas and zones across all intraparietal injections). As expected, the range in distribution as well as density of connections are greater for large injections and injections that included more than one area, and thus must be interpreted with prudence. Despite these technicalities, patterns of connections involving the IPS supported and further detailed the presence of previously proposed cortical networks, including a vestibular network (Fig. 13A), a reaching versus grasping network (Fig. 13B-C), and possibly an auditory-related pathway. With regard to patterns of visual and somatosensory connections, the topographic organization of area VIP is also addressed.

A vestibular network? Graf et al., (1996) reported vestibular sensitivity in over a third of recorded VIP cells. Vestibular responses were associated with visual responses, suggesting that VIP may contribute to the analysis of eye and head motion, and perhaps detect or represent constant spatial coordinates (of the head) in relation to the surroundings. In support of this physiology, VIPm and VIPl (especially anterior portions) received significant inputs from four of the six cortical sites that are known to project

directly to vestibular nuclei (Akbarian et al., 1994), including 7t (roughly 2v), the region of and around 4C (6pa), the Ri/7op/S2 transition region (PIVC), and sometimes 3a (3aV). The above authors have proposed two cortical pathways involving different vestibular nuclei: one primarily involving the oculomotor system (including PIVC, 2v, and 23c/6c), and the other involving cervical motor centers of the spinal cord (6pa and 3aV). The cortical connections of VIP may include both of these networks (Fig. 13A).

Of the above vestibular-related sites described by Akbarian et al., (1994) (which are all characterized by moderately dense SMI-32-ir cell label), the strongest and most consistent VIP projections originated from 7t and 4C. Cortex near the tip of the IPS, near or including 7t, contains cells responsive to vestibular stimuli (also area 2v: Schwarz and Fredrickson, 1971, 1974; Büttner and Büttner, 1978; but also see Grüsser et al., 1990). Additionally, other studies have found cells in this region representing the face and head, being responsive, for example, when the monkey reaches for an object with its lips (Leinonen and Nyman, 1979). Neurons in the vicinity of 4C (subdivision of premotor area 6) are involved with movements of the head, as well as the mouth, forearm, and shoulder (Sessle and Wiesendanger, 1982; Godschalk et al., 1984).

In several cases, moderate to light projections to VIPm and the VIP/AIP transition region originated from area 3a in a location that appears to overlap a vestibular projecting zone (Akbarian et al., 1994: Fig. 12). Light, and less consistent projections to VIP originated from the posterior insular region of the lateral sulcus (Ri, 7op, and S2 region), which overlaps with parieto-insular vestibular cortex (PIVC) of the above authors. PIVC is characterized by cells responsive to vestibular as well as somatosensory stimuli to the neck and shoulder, and visual stimuli such as large-field optokinetic stimulation

(Grüsser et al., 1990). In all VIP injection cases, light to sparse label was observed in zone Toc, which appears to overlap T3 of Akbarian et al., (1994), and is a site that projects directly to the vestibular nuclei. Moreover, VIP may have direct connections with some of the vestibular nuclei (Akbarian et al., 1994: Fig. 3).

Overall, VIP is well connected with most of the above network of vestibular-related cortical areas, and these areas are to varying degrees involved with a diverse range of sensory and/or motor functions involving the face, head and upper limbs. These data are consistent with a role for VIP in comparing movement in one sensory system (such as visual and/or tactile movement) using another system as a reference (vestibular information) (Graf et al., 1996; Duhamel et al., 1997).

Visually guided reaching and grasping networks? Studies of premotor cortex have led to the proposal of separate networks for reaching and grasping with the upper limbs, each of which integrates connections from different portions of parietal cortex (Tanné et al., 1995, Tanné et al., 1996; also see Jeannerod et al., 1995). Differences in the connections of VIP and AIP were consistent with the separation of these two pathways, though there was much overlap (Fig. 13B and 13C). The proposed grasping-related network includes ventral premotor cortex (PMv) (overlapping 6Val and perhaps 4C of this study), and connected areas AIP, 7b (and possibly 7t), anterior area 5, and rostral MIP (Tanné et al., 1996). This collection of areas represent most of the heavily labeled network of areas in one AIP centered injection (Fig. 6), and probably a second, though the frontal lobe was not analyzed (also see Godschalk et al., 1984). Strong connections of AIP with the estimated hand and

digit representations of the S2 complex are also consistent with a grasping related network ('?' in Fig. 13C).

The proposed reaching-related network includes dorsal premotor cortex (PMd), which overlaps 6Ds and dorsal 4C in this study, and connected areas PO, MDP, portions of MIP, VIP, LIP, 7b, and anterior portions of area 5 (Tanné et al., 1996). We found that this collection of areas sent moderate to heavy projections to VIP (with the possible exception of anterior area 5), supporting this network of interconnections.

Within the proposed reaching-related network, areas MDP, PO, most of LIP (posterior LIPd and LIPv), and sometimes 7a projected only or mostly to VIP versus AIP. This organization is similar for the connections described for PMd versus PMv by the above authors. Additionally, area MIP projections were generally stronger to VIP than AIP, and MIP is known to contain cells responsive to active reaching (Colby and Duhamel, 1991). Conversely, relative to VIP, area AIP received stronger projections from 6Val, portions of area 5, and the S2 complex. However, it is not clear how these differences might relate grasping versus reaching per se.

Both VIP and AIP appear to receive strong inputs from the LIP/AIP transition region (disregarding possible tracer leakage artifacts). This region contains hand-movement-related cells and may play a role in the visual guidance of hand movements, especially in matching the pattern of movement with the spatial characteristics of an object that is to be manipulated (Taira et al., 1990; Sakata et al., 1992). Additionally, light to moderate VIP projections also originated from the dorsal portions of the parieto-occipital sulcus in some cases, in the estimated region of V6A. This region contains cells involved in arm-related movements, and possibly visually guided reaching (Galletti et al.,

1996a,b). Thus, anatomically, there would appear to be a large degree of cross-talk between the proposed grasping and reaching networks.

Auditory inputs to the IPS. A major proposed role of parietal cortex is the maintenance of a spatial reference system derived from multiple sensory sources (for review, see Hyvärinen, 1982). Though deep lying areas of the IPS are generally implicated in visual and/or somatosensory representations, moderate to sparse projections to VIP (and possibly AIP, area 5, and LIPv) originated from portions of a swath of auditory-related cortex (Leinonen et al., 1980). In particular, connected areas included a swath of cortex located caudal to primary auditory cortex in the lateral sulcus, across the lobule of the lateral sulcus, and into the dorsal-caudal portion of the STS (Toc and possibly Ri, plus Tpt, and TPOi/TPOc). Relatively light projections to VIP (moderate in one case) were consistently observed from both the ipsilateral zone Toc (immediately caudal to primary auditory cortex), and sparser projections were observed from contralateral Toc (two cases). This region may overlap the portion of Tpt (along the caudal Sylvian fissure) described by the above authors, who found cells selective to the location of sound sources, and suggested that this region (plus Tpt and portions of TPOc/TPOi of this study) may contribute to the spatial control of head movements.

Area VIP, and possibly LIPv, received inputs from the lateral portions of the polysensory region TPOc/TPOi, and at least VIP received contralateral TPOc/TPOi inputs as well. This region overlaps area cSTP of Hikosaka et al., (1988), in which about a third of the recorded cells have either unimodal or multimodal auditory response properties (plus visual and/or somesthetic). Most of these cells were selective to the location of sound, predominantly in the contralateral hemifield. The polysensory integration of cSTP has led to the

proposal that one of the functions of this region is to direct global "attention" to the peripheral environment. Additionally, connections between the IPS and cSTP (and portions of Tpt) may contribute to establishing head, body, and possibly world-centered spatial coordinates for auditory stimuli. The function of auditory-related inputs to VIP remain to be examined physiologically. However, cells in LIP have been found to be responsive to the remembered location of auditory stimuli as well as being responsive to the auditory stimulus itself (Linden et al., 1996; also see Andersen, 1995). Area LIPv and the above mentioned auditory-related areas TPOc and TPOi were at best only lightly connected, possibly conferring these properties.

Other auditory-related cortical regions that projected to VIP and other portions of the depths of the IPS included Ri (Robinson and Burton, 1980), TPOr (Bruce et al., 1981), and possibly area 46 (Tanila et al., 1992), though these connections were often sparse and variable. Together, the above auditory-related areas may constitute a network involved in maintaining a spatial reference system for auditory targets, used for guiding eye movements and limb movements in the extrapersonal space.

Topography of VIP

Cells in area VIP have been reported to show correlations between the location of visual and tactile receptive fields, such that the upper visual receptive fields correlated with upper portions of the face and head (with the mouth being the somatosensory "fovea"), and lower visual receptive fields correlated with lower portions of the face, the neck and in some cells the arm and hand (Colby and Duhamel, 1991; Duhamel et al., 1997). However, the above studies did not show any clear, systematic organization of visual or tactile

receptive field locations, although neurons in the same penetration often had adjacent and/or overlapping receptive fields. The visual connections of area VIP observed in this study are consistent with this organization, as indicated by inputs to restricted portions of VIP from predominantly from either the lower or upper or peripheral visual field representations of several visuotopically organized areas. However, no systematic organization overall was evident. Thus, for area VIP, a rough visuotopic organization can not be ruled out, but our data suggests a patchy organization of visuotopy.

The somatotopic organization of area VIP was also examined. Since over 60% of recorded VIP neurons have tactile receptive fields on the face, head, or neck region (and only a small percentage involving the arm or hand region), connections with the face representation of somatosensory areas was expected (Colby and Duhamel, 1991; Duhamel et al., 1997). However, we found that inputs to VIP originating from several somatotopically organized areas largely included the estimated arm, hand, and digits representations as opposed to the face. These areas include 1, 2, and possibly 3a (Pons et al., 1985), the S2 complex (Burton et al., 1995), primary motor cortex (area 4) (Sessle and Wiesendanger, 1982), and 24d (Luppino et al., 1991). The arm and hand/digit related connections of VIP are consistent with previous connectivity studies. For instance, the fundal region of the IPS has been shown to be connected with the hand region of area 1 (Burton and Fabri, 1995), the arm region of area 1 and 2 (Pearson and Powell, 1985), and the hand/arm representation of area 4 (Leichnetz, 1986). These results suggest that area VIP may contain arm and hand representations in addition to the face and head representation observed physiologically.

The projections to VIP arising from the estimated face representation of somatotopically organized areas include M2 (F3 of Luppino et al., 1991)

(overlapping the supplementary motor area, SMA), and sometimes the S2 complex (ipsilateral and contralateral hemisphere), and possibly 3a and area 4. Strong projections to VIP from regions that contain face-related response properties but lack clear somatotopy include 4C (periarculate cortex, Rizzolatti et al., (1981a) and area 7b (and 7t) near the tip of the IPS (area 7 of Leinonen and Nyman, 1979; Hyvärinen, 1981). The estimated face representations of areas 1 and 2 did not project to area VIP in any of our cases, suggesting that face- and head-related tactile receptive fields of VIP arise through connections with higher somatosensory areas, such as the S2 complex, 7b, 7t, 4C, and possibly area 5. This is somewhat surprising, as many VIP cells are directionally selective and respond to light touch or air puffs, which are stimuli that are also effective for driving cells in areas 1 and 2 (Hyvärinen and Poranen, 1978; Gardner and Costanzo, 1980). The projections from S2 to VIP were sparse to light from the estimated face representation, though may confer some of the face response properties of VIP. However, the connections from S2 to VIP were suggestive of a feed-back projection.

Interhemispheric connections of the IPS and STS

Callosal projecting regions of the macaque cortex tend to be most strongly connected to the corresponding region/area in the opposite hemisphere, being geographically and often topographically homotopic (for review, see Kennedy et al., 1990). This was reported, for instance, for several parietal areas (7a, also PG, Hedreen and Yin, 1981; Andersen et al., 1985; 7a, 7b, 7ip, and 7m, Cavada and Goldman-Rakic, 1989a,b). As anticipated, the callosal connections of the IPS and STS areas we studied appeared to be most

concentrated in cortex that was architectonically homotopic with the location of the corresponding injection sites.

The heterotopic callosal connections of areas VIPl, VIPm, LIPv, AIP, and MSTdp largely mirror the corresponding distribution of label in the ipsilateral hemisphere (as well as relative density), though contralateral labeling density was consistently lower, consistent with other studies (cf. Cavada and Goldman-Rakic, 1989b). However, deviations from this organization were evident in some instances. For example, disproportionately strong callosal projections to VIPm were observed from MDP and Toc in one case (Fig. 7). Also, FST callosal projections to MSTdp were very light (insignificant) while the ipsilateral projections were very dense (cf. Figs. 6 and 7). These patterns of label may be particular to the portions of each area injected and not the area as a whole, as many areas show gradients of callosal projecting cell densities within their areal boundaries (cf. Andersen et al., 1985; Maunsell and Van Essen, 1987).

As with intrahemispheric connections, interhemispheric connections in the macaque have been shown to follow a similar classification scheme for feed-forward and feed-back patterns of connections (cf. Kennedy et al., 1986). It has been suggested that the laminar pattern of callosal projecting cells is more restricted to layer 3 (or 3b), having disproportionately fewer cells in layers 2, 5 and 6 (Hedreen and Yin, 1981; Andersen et al., 1985; Kennedy et al., 1986). This might signify different criteria for assessing the hierarchical relationships of areas. However, we found label almost exclusively in infragranular layers in a few regions, suggestive of feed-back projections. They include TPOc feed-back projections to contralateral MSTdp (Fig. 7), and S2 (and S2/7op transition region) feed-back projections to contralateral VIPl, which are hierarchical relationships that are consistent with those of the ipsilateral hemisphere as mentioned earlier.

On a technical note, it was tempting to interpret the dense homotopic labeled fields in the contralateral hemisphere as representing an upper bound estimate of the extent of the effective tracer uptake zones in the ipsilateral hemisphere. However, at least in other mammalian species, some areas have their most concentrated callosal connections with anatomically heterotopic portions of the contralateral hemisphere. For instance, in the rat, connections of the central visual field representation in area V1 (the binocular zone), connections between the striate cortices interlink corresponding regions of the visual field, which are not mirror-symmetric in the two hemispheres about the midline, but rather heterotopic. However, connections of the peripheral visual field representations are homotopic with contralateral V1, being mirror-symmetric about the midline (Lewis and Olavarria, 1995). Thus, exceptions from the strong geographically homotopic connections are demonstrable in mammals, and thus in this study we avoided interpreting the callosal connection patterns in this regard.

Functional implications/significance

From physiological studies, area VIP is believed to be involved in the multisensory analysis of stimulus motion, especially in the near personal space, and may contribute to eye/hand and mouth coordination (Colby et al., 1993a; Duhamel et al., 1997). The connections of the VIP are consistent with these functions, though they suggest a stronger somatomotor component involving the arm, hand, and digits than has previously been described (ibid.). Such involvement may be related to visually-guided reaching (and grasping), as VIP is strongly connected with many cortical regions known to be involved

in reaching and grasping, including motor and dorsal premotor cortex (cf. Tanné et al., 1996).

Projections from auditory-related areas to the fundus region of the IPS suggest that VIP may be responsive to the location of auditory stimuli. Response properties may be similar to those described for LIP, in which the location in space of an auditory target appears to be stored by LIP neurons (Andersen, 1995; Linden et al., 1996). Projections to VIP also included vestibular-related cortical areas and the head representation of several areas high in the cortical hierarchy. These connections may be involved with representing the space immediately surrounding the head and face, which is consistent with lesions of VIP that result in behavioral deficits selective for near stimuli (Duhamel et al., 1997). Specifically, VIP may be involved with exploratory movements with the mouth and face, as has been suggested for a portion of area 7b (Leinonen and Nyman, 1979), which was found to have strong and consistent connections with VIP. Overall, VIP appears to be connected with a wide range of functional networks that may be integrated to maintain a spatial reference system that can be used for guiding limb and face movements.

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Chapter 4: General Discussion

The results from the preceding two chapters demonstrate architectonic and connectivity support for a large number of previously described cortical areas as well as newly described zones throughout the hemisphere of the macaque, especially with regard to areas of parietal cortex and the intraparietal sulcus (IPS). The results of this thesis, combined with previous physiological and behavioral studies, have implications for the function of VIP and surrounding cortical areas, and may also serve as a guide for future physiological and connectivity studies.

Functional roles of VIP

A major finding of this study is that the fundal region of the intraparietal sulcus (IPS), area VIPm and VIPl, have substantial connections with visual, somatosensory, polysensory, oculomotor, somatomotor, and vestibular-related cortex, and possibly auditory cortex. This widespread pattern of connections is consistent with proposed functions of parietal cortex in general, including the task of maintaining a spatial reference system for the animal, which is used for guiding eye movements and somatic movements in the extrapersonal space (for review, see Hyvärinen, 1982). This role for parietal cortex was originally based on the combined functions of multiple parietal areas, including areas 5 and 7 (lesion studies and physiology mentioned in Chapter 1). However, the widespread connections of area VIP and possibly a network of several bimodal areas including MIP, MDP, the AIP/LIP transition region and 7b may more accurately reflect those areas that truly integrate the different modalities in the parietal lobe.

Connections of cortex surrounding VIP show considerable contrast in the overall patterns of label, which argues against their involvement as central areas for the bimodal integration of the visual and somatosensory modalities. For instance, area AIP (anterior and lateral to VIP) shows relatively sparse visual-related connections, and conversely neighboring area LIPv (lateral and dorsal to VIP) has relatively few somatosensory and somatomotor connections. The connections of two other areas bordering VIP (PIP and 5V) were not injected with tracers in this study. However, based on the patterns of projections we observed from these regions, PIP appears to be purely visual-related, and 5V largely sensorimotor-related. The posterior-medial border of VIP is shared with area MIP. Based on the visual and somatosensory projections of this area, as well as strong connections with bimodal area VIP, MIP is likely to show a wide spread constellation of connected areas throughout the hemisphere.

VIP appears to be involved in a number of cortical networks as discussed in Chapter 3, including a reaching (versus grasping) network that may involve eye/hand and mouth coordination, a vestibular-related network, and an auditory network. These networks may all be related to establishing and maintaining a spatial reference system that incorporates objects in the environment (auditory, visual, and somatosensory inputs) as well as movements of the body and head (vestibular and somatomotor inputs). How the connections of this complex system might be organized is presently not clear, though somatotopy has been suggested (Graziano and Gross, 1993). Several regions of the macaque brain exhibit bimodal response properties similar to those reported for VIP (Colby and Duhamel, 1991), and have been found to contain at least a rough somatotopic organization (arm and face), including inferior area 6 (F4 and F5 of Rizzolatti et al., 1981a, b), 7b

(Hyvärinen and Poranen, 1974; Leinonen and Nyman, 1979; Leinonen et al., 1979; Robinson and Burton, 1980; Hyvärinen, 1981), and the putamen (Graziano and Gross, 1993). These areas, except for VIP, have been shown to contain at least varying degrees of somatotopic organization including head and arm representations. Thus, at least superficially, it seems plausible that architectonically defined VIP may contain an arm/hand as well as face representation.

Consistent with this hypothesis, we observed a bias of VIP connections with the arm, hand and digits representations as opposed to the face, especially in areas 1/2, 4, 24d, and possibly S2. The relatively stronger arm and hand versus face connections of VIP seem at odds with the known somatosensory properties of VIP. For instance, roughly three quarters of VIP neurons were found to be independently driven by stimulation of somatosensory receptive fields found primarily on the face and head (Colby and Duhamel, 1991; Duhamel et al., 1997). Also, some trajectory neurons respond best to a visual stimuli moving toward the animal, particularly when the anticipated point of contact of the stimulus is on a region of the animal's face (Colby et al., 1993).

The lack of projections to VIP from the face representation of area 2 is perplexing, given the similar somatosensory response properties of both of these areas. Instead, the face representation inputs may originate from S2, 7b, 7t, M2, or possibly area 5. However, all of the above areas, except for area 5 are thought to be higher in the cortical hierarchy than VIP (including S2 based on connections observed in this study), and thus they would represent feed-back connections rather than inputs (cf. Van Essen et al., 1990). Hence, the origin of face-related response properties has yet to be established.

One possibility is that our injections were located in portions of VIP further anterior to typical recording sites of VIP, and that architectonically

defined area VIP may prove to be connected with area 2. If this pathway does not exist, however, it would be interesting to speculate why the face tactile response properties of VIP appear to originate from somatosensory areas higher than area 2 in the somatosensory hierarchy, whereas the hand and arm representation of area 2 sends inputs directly to VIP. One possibility is that exploration of objects in the environment with the hands and arms (with or without visual input) may serve to "map out" the spatial environment, and thus be important to convey to the fundus of the IPS to integrate with other senses.

FUTURE DIRECTIONS

As is often this case with studies such as this one, the results led to more questions than answers. In particular, several areas or regions may prove readily accessible for further connectivity and physiological study. For instance, within the IPS, the newly defined zones LOP (formerly V3A) and 7t (formerly 2v or part of 7b) are relatively easy to identify architectonically, thereby providing an independent means for evaluating functionality (visual and vestibular, respectively). Additionally, addressing any physiological differences between medial and lateral portions of VIP may prove to correlate with the myelin and SMI-32-immunoreactive cell label gradients observed across the fundus.

Within the superior temporal sulcus, a sharper physiological distinction between polymodal area TPOc and visual-related area MSTda seems addressable. In some parietal injection cases, both TPOc and MSTda appeared to contain a shared heavy labeled fields, while in other injections, a visual versus bimodal distinction in labeled fields was evident.

From frontal cingulate cortex, nearly all parietal injections received inputs from area 24b. This region is largely implicated in premotor functions, though is not somatotopically organized (Luppino et al., 1993). The fact that a portion of one small cortical region appears to connect with much of parietal cortex is more an exception than a rule. Better establishing the organization (i.e., confirming with injection in 24b) may provide further insight as to the function of 24b.

Subcortical connections. Projections to the IPS from the thalamus and claustrum were charted in most cases in this study, though the one in six sampling for histological stains was suboptimal for identifying cortical nuclei and the small labeled fields within the pulvinar (thalamus). Projections from pulvinar and claustrum were moderate to strong, as has been observed in other studies of parietal cortex (cf. Baizer et al., 1993). In the thalamus, labeled fields from multiple injections of the parietal lobe (viewed in 3D) revealed a complex mosaic of partially overlapping patches. However, further analysis and interpretation of the thalamocortical pathway with VIP and other parietal areas will require denser histological sampling to better reveal the structural compartments of the thalamus. Connections with the claustrum were consistent with those observed by Baizer et al., (1993). Some of the vestibular nuclei are likely to be connected with area VIP, and is worth further examination (cf. Akbarian et al., 1994).

Morphing and databases. A major problem with comparing the morass of detailed connectivity data from other studies of the macaque is use of different formats. This problem can to a large extent be overcome by predominant use of one representation, such as the flat map, which has

steadily evolved as a preferred format for viewing a large array of cortical data (cf. Drury et al., 1996a). Even if detailed architectonic parcellations are not feasible in some studies, viewing labeled fields with respect to cortical sulci has proven informative for comparing with other studies (at least in the macaque), especially on the flat map representation. Additionally, a surface-based transformation of one cortical map can be made to match the shape of another, as is done with MapWarp (Drury et al., 1996b, 1997). Geographic landmarks (fundi and sulcal ridges) and/or architectonic landmarks can be used to drive the deformations, while cell data are passively remapped to conform to the target map. This approach to data representation is well suited for inclusion into a grand database of connections for the macaque monkey, and may one day allow for an easily accessed database of the neural connections that underlie the function of primate cerebral cortex.

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