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Cortical Connections of Area V4 in the Macaque

Leslie G. Ungerleider[1], Thelma W. Galkin[2], Robert Desimone[2,3] and Ricardo Gattass[4]

[1]Laboratory of Brain and Cognition, [2]Laboratory of Neuropsychology, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892 USA, [3]McGovern Institute, MIT, Cambridge, MA, USA and [4]Instituto de Biofísica Carlos Chagas Filho, UFRJ, Rio de Janeiro RJ 21941-941, Brazil

To determine the locus, full extent, and topographic organization of cortical connections of area V4 (visual area 4), we injected anterograde and retrograde tracers under electrophysiological guidance into 21 sites in 9 macaques. Injection sites included representations ranging from central to far peripheral eccentricities in the upper and lower fields. Our results indicated that all parts of V4 are connected with occipital areas V2 (visual area 2), V3 (visual area 3), and V3A (visual complex V3, part A), superior temporal areas V4t (V4 transition zone), MT (medial temporal area), and FST (fundus of the superior temporal sulcus [STS] area), inferior temporal areas TEO (cytoarchitectonic area TEO in posterior inferior temporal cortex) and TE (cytoarchitectonic area TE in anterior temporal cortex), and the frontal eye field (FEF). By contrast, mainly peripheral field representations of V4 are connected with occipitoparietal areas DP (dorsal prelunate area), VIP (ventral intraparietal area), LIP (lateral intraparietal area), PIP (posterior intraparietal area), parieto-occipital area, and MST (medial STS area), and parahippocampal area TF (cytoarchitectonic area TF on the parahippocampal gyrus). Based on the distribution of labeled cells and terminals, projections from V4 to V2 and V3 are feedback, those to V3A, V4t, MT, DP, VIP, PIP, and FEF are the intermediate type, and those to FST, MST, LIP, TEO, TE, and TF are feedforward. Peripheral field projections from V4 to parietal areas could provide a direct route for rapid activation of circuits serving spatial vision and spatial attention. By contrast, the predominance of central field projections from V4 to inferior temporal areas is consistent with the need for detailed form analysis for object vision.

Keywords: extrastriate cortex, inferior temporal cortex, object recognition, primates, visual system

Introduction

The organization of the topographic map in V4 (visual area 4) has been studies by anatomical and physiological methods. Zeki (1969) first described the prelunate gyrus and adjacent cortex in the macaque as a region that receives projections from the central visual field representations of V2 (visual area 2) and V3 (visual area 3). He divided this region into area V4, located in the anterior bank of lunate sulcus, and V4A, located on the prelunate gyrus. Subsequently, Van Essen and Zeki (1978) named the entire region the "V4 complex" because each point from the central 10° of the lower visual field was represented multiple times in the region. Zeki (1978) extended his recordings medially from the prelunate gyrus into the posterior bank of the superior temporal sulcus (STS) into an area that is lateral to area MT (medial temporal), and he included this lateral region in the V4 complex as well. Maguire and Baizer (1984) later named this lateral region V4t (V4 transition zone). These investigators also noted that the visual field representation on the prelunate gyrus extended up to 30° in the lower visual field. In subsequent physiological recordings, Gattass et al. (1985, 1988) explored the ventral aspect of the hemisphere and redefined V4 as a dorsoventral strip of cortex containing the representation of the central 30–40° of the visual field, with the upper visual field represented ventrally and most of the lower visual field represented dorsally (a small and variable portion of the lower visual field was mapped ventrally at the anterior border of V4).

Subsequent work demonstrated that the physiological response properties of V4 neurons are related to their connections. V4 receives inputs from both cytochrome *c* oxidase (CO)–rich thin stripes and CO-poor interstripe regions of V2 and has both color- and form-selective cells, as well as many cells selective to both features (DeYoe and Van Essen 1985, 1988; Desimone et al. 1985, 1992; Shipp and Zeki 1985, 1989; Desimone and Schein 1987; Zeki and Shipp 1988, 1989; Schein and Desimone 1990; Van Essen et al. 1991; Nakamura et al. 1993). V4 appears to have a modular organization (DeYoe and Van Essen 1988; Yoshioka et al. 1992; DeYoe et al. 1994; Felleman, Xiao, et al. 1997; Xiao et al. 1999; Tootell et al. 2004); however, the geometry of the modules as well as their relation to color and form analysis are still unknown. The major outputs of V4 are to areas TEO (cytoarchitectonic area TEO in posterior inferior temporal cortex) and TE (cytoarchitectonic area TE in anterior temporal cortex) in the inferior temporal cortex (Desimone et al. 1980; Ungerleider 1985; Weller and Kaas 1985, 1987; Weller and Steele 1992; Distler et al. 1993), which contains neurons selective for object features, such as color, shape, and texture (Desimone et al. 1984; Tanaka et al. 1991; Fujita et al. 1992).

Although considerable progress has been made in delineating the anatomical connections of the central 5–6° of the visual field in V4, little is known of the connections beyond this eccentricity. The goal of the present study was therefore to delineate the complete set of inputs and outputs of V4, from central to peripheral field representations in both the upper and lower visual fields. Inasmuch as we previously found that central and peripheral field representations of V2 project to different target areas (Gattass et al. 1997), we were especially interested in determining whether this would also be true for V4. We report here on the cortical connections of area V4 in 9 monkeys with multiple injections (n = 21) of anterograde and retrograde tracers placed under physiological control into different retinotopic locations; our injections were large enough to include all the functional subregions within V4 at a given eccentricity (e.g., see Felleman, Xiao, et al. 1997; Xiao et al. 1999).

Materials and Methods

Material from 9 adult *Macaca mulatta*, weighing between 3.2 and 4.4 kg, was used. In all animals, injections of tracers were placed into retinotopically specified sites ($n = 21$) in V4, which were determined by electrophysiological recordings. The injection sites, 2 or more in each animal, spanned eccentricities from central to peripheral vision in both the upper ($n = 4$) and lower ($n = 17$) visual field representations (Gattass et al. 1988). All experimental procedures followed the National Institutes of Health Guide for the Care and Use of Animals and were approved by the National Institute of Mental Health Institutional Animal Care and Use Committee.

Receptive Field Recording

Animals were surgically implanted with a headpost and recording chamber, and the recordings and injections were made several days to weeks later. All of the methods for surgery, anesthesia, and recording of receptive fields have been described in detail previously and will not be repeated here (Desimone and Gross 1979; Gattass and Gross 1981; Gattass et al. 1987, 1988, 1990).

Injections of V4

Pressure injections onto the cortical surface were made using a 1-μL Hamilton syringe with a beveled 27-gauge needle, which was guided into the appropriate site with the aid of an operating microscope. In 7 animals, the injections were placed at physiologically determined sites on the prelunate gyrus under direct visualization of the cortex. In the remaining 2 animals, after the desired injection site was located electrophysiologically, a guide tube was advanced through the dura and placed about 300 μm above the intended injection site. The microelectrode was then advanced through the guide tube and the visuotopic location of the injection site was confirmed. The electrode was then withdrawn from the guide tube and replaced by a 1-μL Hamilton syringe. In 9 animals, we injected 0.15–0.3 μL of an equal-parts mixture of tritiated proline (New England Nuclear L-[2,3,4,5-3H], specific activity 100–140 Ci/mmol) and tritiated leucine (New England Nuclear L-[3,4,5-3H(N)], specific activity 100–140 Ci/mmol). The labeled amino acids (^{3}H), which had been evaporated and then reconstituted in 0.9% saline to give a final concentration of 50 μCi/μL, were injected at the rate of 0.02 μL/2 min. To minimize leakage of the tracer up the electrode track, the syringe was left in place for 30 min after the injection and then withdrawn into the guide tube, which was then removed from the brain. In 5 animals, 1–3 injections (0.15–0.3 μL each at each site) of aqueous solutions of 2% Fast Blue (FB), 4% Diamidino Yellow (DY), and/or 10% Bisbenzimide (Bis) were placed in a given site in V4. In 6 animals, 2–4 injections, 0.2 μL each of 5% wheat germ agglutinin conjugated to horseradish peroxidase (HRP), were placed in V4. In cases of combined injections of HRP with ^{3}H or fluorescent dyes, the ^{3}H and dyes were injected into the cortex in one procedure, and, 4 days later, the HRP was injected in a second procedure. A list of cases and tracers is shown in Table 2.

Histological Processing

After survival times of 6–8 days following injections of ^{3}H and fluorescent dyes (and 2 days after the HRP injection), the animals received a lethal dose of sodium pentobarbital and were then perfused transcardially with 0.9% saline followed by 10% formaldehyde–saline. Their brains were blocked with the aid of a stereotaxic apparatus, removed from the skull, photographed, and stored in 30% sucrose in 10% formaldehyde–saline until they sank. Frozen sections, 33 μm in thickness, were cut in the frontal plane. Every fifth section was mounted onto gelatinized slides, dehydrated, defatted, and processed for autoradiography according to the procedures of Cowan et al. (1972). The sections were dipped in Kodak NTB2 emulsion and exposed at 4 °C for at least 12 weeks. Subsequently, the autoradiographs were developed in Kodak D19, fixed, and counterstained with thionin. Alternate sections were stained for myelin with the Gallyas (1979) method. Another series of sections were processed for HRP histochemistry according to a modified tetramethylbenzidine protocol (Gibson et al. 1984). The remaining sections were mounted and coverslipped unstained for subsequent analysis of fluorescent labeling. For purposes of analysis, the locations of concentrations of silver grains, HRP-labeled cells and terminals, and fluorescent-labeled cells were charted onto enlarged photographs of the myelin-stained sections.

Assignment of Label to Specific Visual Areas

For each case, a 2-dimensional map of the cortex was generated (Ungerleider and Desimone 1986; Gattass et al. 1987). The locations of the tracers, myeloarchitectonic borders, and recording sites were transferred onto the flattened maps. In one case (Case 5) it was not possible to obtain a reliable myelin stain of a series of sections. In this case, we estimated the borders based on the known average width of the areas in the flattened maps. We used myeloarchitectural differences to distinguish areas V2, V3, PO (parieto-occipital area), V4, V4t, LIPv (ventral portion of lateral intraparietal area), LIPd (dorsal portion of LIP), MT, TEO, and the densely myelinated zone of MST (medial STS area). Numerous published papers illustrate the myeloarchitectural appearance of these areas (e.g., see Ungerleider and Desimone 1986; Boussaoud et al. 1990; Colby et al. 1993; Distler et al. 1993; Webster et al. 1994; Gattass et al. 1997; Lewis and Van Essen 2000). The location and the extent of the visual cortical areas just described are illustrated in a 2-dimensional reconstruction of the macaque extrastriate cortex in Figure 1.

To access the reliability, strength, and type of V4 connection with each cortical area, 2 investigators independently analyzed the anterograde and retrograde data that had been charted onto the photographs of myelin-stained sections. For each case, the relative strength of the connection was qualitatively classified as strong (+++), medium (++), or weak (+). Depending on the laminar distribution of the cells and terminals, each connection was also classified as feedforward, intermediate, or feedback. Tables 1 and 2 present these quasi-quantitative evaluations for each projection.

Results

The results are based on data from 21 injections of anterograde and retrograde anatomical tracers into V4. We will first present an overview of the connections of V4 with occipital, temporal, and parietal lobe areas. For each of these areas, we will describe the laminar distributions of labeled cells and terminals and these will be related to inputs and outputs of V4. We will then describe differences in the topology of the connections between V4's upper and lower visual field representations. Next we will demonstrate differences in the connections between central and peripheral field representations of V4, and we will illustrate those differences with data from individual cases. Finally, we will describe the topographic connections of V4 with a region in prefrontal cortex.

Injection Sites in V4 and Connections with V2 and V3

Figure 2 summarizes on a flattened map of extrastriate cortex the injection sites in area V4 and the topographic organization of the connections with V2 and V3 (for clarity, only 17/21 of the cases are illustrated; see Table 1 for the data from the remaining cases). The injections sites ranged from the fovea of V4 to eccentricities of 30° in the lower visual field and to eccentricities of 20° in the upper visual field. In all cases, there were one or more labeled zones in V2 whose visuotopic locus was highly consistent with the visuotopic locus of the injection site in V4 (Gattass et al. 1988). With the exception of injection site 6, all injections also showed topographically organized connections with V3. Injection sites numbered 1 through 13 were located in the prelunate gyrus at progressively more peripheral locations in the lower visual field, and connections resulting from these injections were found at progressively more dorsomedial locations in V2 and V3. Similarly, injection sites 15–17 were located on the ventral aspect of the hemisphere at progressively more peripheral locations in the upper visual field, and the connections resulting from these injections were found at progressively more ventromedial locations in V2 and V3.

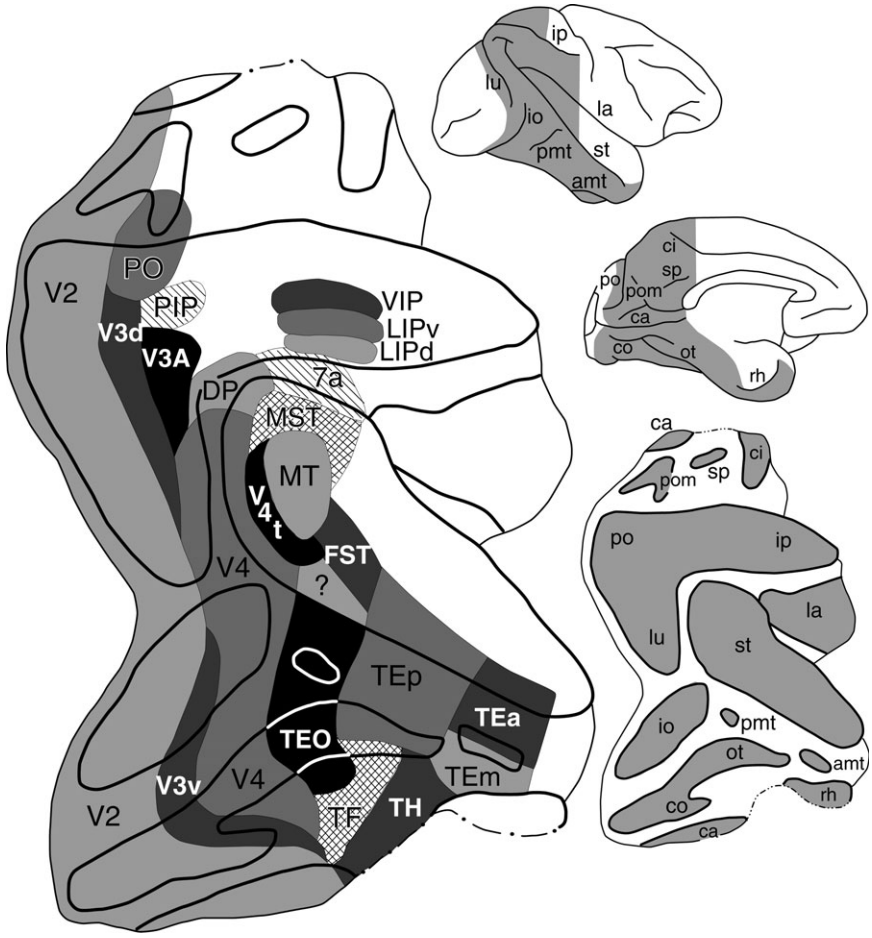

Figure 1. Two-dimensional reconstruction of the macaque cortex, showing the location of the extrastriate visual areas found to be connected with V4. Heavy lines indicate the boundaries of the sulci, and the dotted–dashed lines indicate the boundaries between the neocortex and allocortex. The gray area on the lateral and medial surface views of the hemisphere (upper right) indicates the region represented in the 2-dimensional reconstruction, whereas the gray areas on the small 2-dimensional reconstruction (lower right) indicates cortex within sulci. For names of areas and sulci. Abbreviations: amt, anterior middle temporal sulcus; ip, intraparietal sulcus; io, inferior occipital sulcus; la, lateral sulcus; lu, lunate sulcus; pmt, posterior middle temporal sulcus; st, superior temporal sulcus; ci, cingulate sulcus; sp, subparietal sulcus; pom, medial parieto-occipital sulcus; ca, calcarine fissure; co, collateral sulcus; ot, occipitotemporal sulcus; rh, rhinal sulcus.

Injection site 14 was located at the fovea on the representation of the horizontal meridian, resulting in dorsal and ventral patches in both V2 and V3. The connections with V2 consisted of multiple patches of label, which appeared to be more spatially separated than those found in V3. Unlike the connections with dorsal V2 and V3, the patches within ventral V2 and V3 extended continuously across the border separating the 2 areas. Thus, they included the representation of the horizontal meridian that forms the border between the 2 areas (Gattass et al. 1981, 1988), although the injection sites in ventral V4 were located well inside the area, away from its anterior border. This finding is consistent with the notion that the representation of the horizontal meridian in dorsal V4 is located at its anterior border, but within ventral V4 it is located within the area at eccentricities beyond 4° and 5° (Gattass et al. 1988, 1997). A comparison of the receptive fields recorded at the V4 injection sites with the estimated visual field representations of the locations of connections with V2 and V3 indicates a good agreement between the 2 (Gattass et al. 1981, 1988).

Not illustrated in Figure 2 are V4's connections with V1 (primary visual cortex). Of the 21 V4 injections, 6 showed labeled terminals in V1 and 2 showed labeled cells.

Feedback and Feedforward Connections of V4: Laminar Distribution of Cells and Terminals

It has been proposed that feedforward projections from lower-order cortical visual areas originate mainly in layer III and terminate predominantly in layer IV, whereas feedback projections from higher-order areas to lower-order ones originate mainly in layers V and VI and terminate above and below layer IV, avoiding this layer (Rockland and Pandya 1979; Maunsell and Van Essen 1983c). Maunsell and Van Essen also described an additional anterograde projection pattern that they called intermediate in that was not clearly either feedforward or feedback; intermediate-type connections are characterized by terminal patches that vary from one type to another or the terminals are homogenously distributed across all layers, including layer IV, but are not heaviest in layer IV. Finally, Felleman and Van Essen (1991) also described a bi-laminar pattern of projecting neurons, which could characterize the origin of either feedback, feedforward, or intermediate type of connections; the direction of anatomical "flow" for this bi-laminar pattern can be disambiguated with anterograde data.

Based on these distinctions, and a combination of retrograde and anterograde data, we were able to categorize the

Table 1
Strength of the connection with V4[a]

Cases	ECC	Tracer	Occipital areas					Posterior STS areas				Temporal areas					Parietal areas						Frontal
			V1	V2	V3	V3A	DP	V4t	MT	FST	MST	TEO	TEp	TEm	TEa	TF	LIPv	LIPd	VIP	PIP	PO	7a	FEF
1c and p	−2 to −15	^{3}H	++	++	+++	++		+++	+	++		+++	+++		+	+	+	++					+
3c	−3	^{3}H	++	+++	+++	+		+++	+++			+++	+++			+		+					+
8c	−8	^{3}H	+	++	+	++		+++	+++		+	++	++	++	+	++	+++	+++					+
9c	−8	^{3}H		+				+	+			++	+++										+
2p	−16	^{3}H		+++	++	++		++	++			++	+++										++
4p	−18	^{3}H	+	+++	+++	+++		++	+	+		++	+++	+				++	+				++
1p	−22	^{3}H	+	++	+++	+++		+	+++	+		+	++	+		+	++	+		++	++	+	+
7p	−25	^{3}H		+	+	+			+			+					++	+++					+
5p	10	^{3}H		+	++				++	++		+											
8c	−1	FB	+	+++	+	+		+	++	+		++	++	+	+	+							+
4c	−2	FB		+++	+++			+	++	+		+++	++	+			+						+
5c	−4	FB		++	+			+	++			+	+	+		+	+						+
3p	−10	Bis		+++	+	++	+	+	+	++		++	+	+		+	+++	+		+	+		+
4p	−18	DY	+	+++	++	++	+	+	++	+		+	+	+			+	+	+	+	+		+
7p	−25	Bis		+++	+++	+		+	++	+	+	++	+	+	+	+	+	+	+	+	+	+	++
4c	−1	HRP		+	+			+	++	+		++	+				+						+
2c	−2	HRP		+++	++			++	+			+++	++		+	+	++						+
3p	−8	HRP		++	++	+	+	+	+	+		+++	+++	+		+	+	+++				+	++
8p	−30	HRP		++	++	+	×	+	+++	+		+++	++			+	+	++	+		+	+	
5c	4	HRP		++	+			+	+	+++		++	++		+		+++	++					+
6p	20	HRP	++	+++	+++	++		+	++	++	+	+++	+	+	+	+++	+++	++	+	+	+		+

[a]+, light; ++, moderate; +++, heavy; c, central field injection; p, peripheral field injection; ×, relevant sections not analyzed; ECC, eccentricity; ^{3}H, labeled amino acids.

Table 2
Laminar distribution of cells and terminals after V4 injections[a]

Cases	ECC	Injections	Occipital areas					Posterior STS areas				Temporal areas					Parietal areas						Frontal
			V1	V2	V3	V3A	DP	V4t	MT	FST	MST	TEO	TEp	TEm	TEa	TF	LIPv	LIPd	VIP	PIP	PO	7a	FEF
Anterograde tracer in V4																							
1c and p	−2 to −15	^{3}H	B	B	I	B, I		I		F		F	F		F		I	F					I
3c	−3	^{3}H	B	B	B	I		F, I	F			F	F	F		F	F	F					I
8c	−8	^{3}H	B	B	I, F	I		F, B	I, B		F	F	F	F	F	F	I, F	I, F					I, B
9c	−8	^{3}H		B				I	I			F	F										×
2p	−16	^{3}H	B	B	B	B, I		F	F			F	F				I	F					I
4p	−18	^{3}H	B	B	B	B		I	I	F		F	F	F				F	I		F		I, F
1p	−22	^{3}H		B	B	B		I	F	F	F	F	F	F		F	F	I		I	I	F	I, F
7p	−25	^{3}H		B	B	B, I			F			F					F	F					I
5p	10	^{3}H		B	B				F			F											
4c	−1	HRP																					
2c	−2	HRP		B	B			I	I			F	F				I						I
3p	−8	HRP		B	I	I	I	I	I	F		F	F	F		F	F	F				F	I
8p	−30	HRP		B	B	I	×	I	I	I		F	I			I	I	I	I		I	F	F
5c	4	HRP		B	F			I	I	I		I	F		I		B	I	I				B
6p	20	HRP	B	B	I	I		F	F	F	F	I	I	I	I	I	I	F	F	F	F		I
		overall	B	B	B	I	I	I	I	F	F	F	F	F	I	F	F	F	I	I	F	F	I
Retrograde tracer in V4																							
Cases	ECC	Injections	V1	V2	V3	V3A	DP	V4t	MT	FST	MST	TEO	TEp	TEm	TEa	TF	LIPv	LIPd	VIP	PIP	PO	7a	FEF
8c	−1	FB	s	s, =	=	=		i, s	i			=, i	i, =	i	i	i							i
4c	−2	FB		s	=			i	i, s	i, =		=	i, =	i			i						i
5c	−4	FB		s, =	=			=	i, =	i		1, =	i, =	i		i	i						i
3p	−10	Bis		s	s	=	i	=	=, i			1, =	i	i		i	i, =	i		i	i		i
4p	−18	DY	s	s	s	=	i	=	i, =			i	=, i	i			i	i	=	i	=		s
7p	−25	Bis		s	s, =	=	i	s	=	=	s	=	i	s, =	s	i	=	=	=	s	=	=	=, i
4c	−1	HRP		=	=			i	=	i		=	i				s						s
2c	−2	HRP		s	s			=	=			i	i			i	=	i					s
3p	−8	HRP		s	s	s		i	i	i		i	i	=			i	i				i	s
8p	−30	HRP		s	s	=	×	s	s, =	s		=	i			i	i	I, =	=		=		i
5c	4	HRP		s	i			=	=	s		=	i				=	=					
6p	20	HRP		s	s	=		s	s	s	s	=		i	i	i	s	s	s	s	s		s
		overall	s	s	s	=	i	=	=	i, s	s	=	i	i	i	i	i	i	=	i, s	=	i, =	i

[a]B, feedback projection; I, intermediate-type projection; F, feedforward projection; s, cells mainly in superficial layers; i, cells mainly in infragranular layers; =, cells in both superficial and infragranular layers; c, central field injection; p, peripheral field injection; ×, relevant sections not analyzed; ECC, eccentricity; ^{3}H, labeled amino acids.

connections of V4 as feedback, intermediate, or feedforward in each of the cases. The results are illustrated in Figure 3*A* and are summarized, case by case, in Table 2. The connections of V4 with V2 and V3 were classified as "feedback". In both V2 and V3, retrogradely labeled cells were located predominantly in the supragranular layers and the anterogradely labeled terminals were located in layers I and VI, avoiding layer IV. The assignment of the label to the category "feedback" was more consistent across cases for V2 than for V3 (see Table 2). In those cases showing label in V1, the projection was clearly feedback

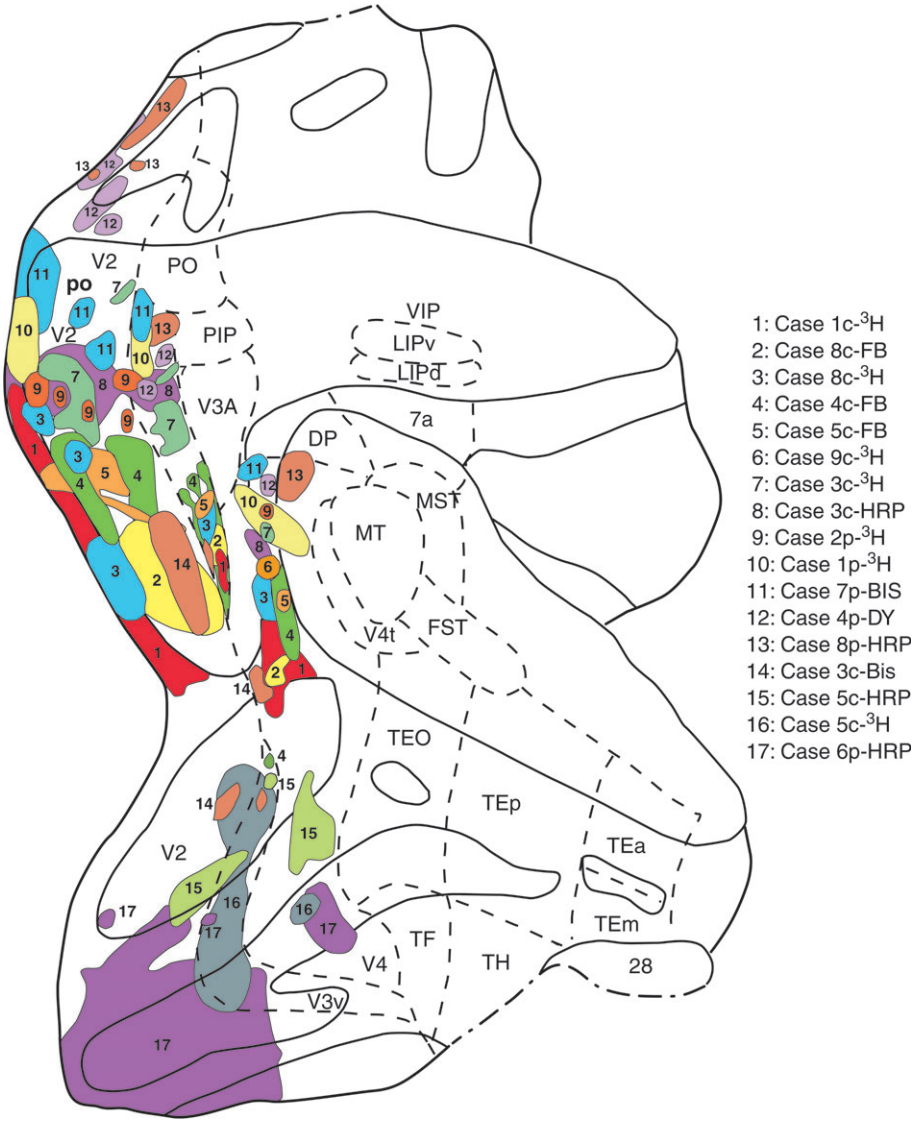

Figure 2. Injection sites and feedback projections of V4, shown on a 2-dimensional reconstruction of the extrastriate cortex. Each injection site and its corresponding connections with V2 and V3 are numbered and colored accordingly. Myeloarchitectonic borders of visual areas are indicated with dashed lines. The projections from the individual cases were plotted on this map to best retain their locations relative to myeloarchitectonic borders and sulci. For other conventions, see Figure 1.

from V4. Intermediate-type connections with V4 were found in V4t, V3A (visual complex V3, part A), DP (dorsal prelunate area), PIP (posterior intraparietal area), VIP (ventral intraparietal area), and the FEF (FEF not illustrated in Fig. 3*A*). In these areas, retrogradely labeled cells were located both above and below granular layer IV, and the anterogradely labeled terminals generally included all cortical layers, including layer IV. However, in both V3A and the FEF, some patches of label were also characteristic of feedback and feedforward connections, respectively. Feedforward projections from V4 were found in MT, MST, FST (fundus of the STS area), TEO, TE (including TEp [posterior portion of area TE], TEm [medial portion of area TE], and Tea [anterior portion of area TE]), TF (cytoarchitectonic area TF on the parahippocampal gyrus), LIP (LIPv and LIPd), PO, and 7a. The connections of 5 of 15 anterograde cases in MT and 2 of 7 in FST appeared to be intermediate rather than feedforward, but for the remainder of the areas the feedforward pattern was more consistent.

Figure 4*A* shows a photomicrograph of a case (Case 2c) with an injection of HRP in V4 at an eccentricity of 2° in the lower visual field. The resulting cells and terminals in V2 and in TEO and TEp are shown in Figure 4*B*,*C*, respectively. In V2, we observed labeled cells in layer III and terminals in layer I and, more extensively, in layers V/VI, indicative of a feedback projection from V4. The labeled cells and terminals in V2 were patchy and in register (see also Fig. 6). In TEO and TEp, we observed labeled cells in layer VI and terminals in layer IV, indicative of a feedforward projection. In TEp, the terminals extended from layer IV to the more superficial layers.

Connections with Upper and Lower Field Representations of V4

The summary of the projection fields of V4 from its upper and lower visual field representations is shown in Figure 3*B*. Projections from the upper field of V4 to V2 and V3 were located ventrally, whereas projections from the lower field of

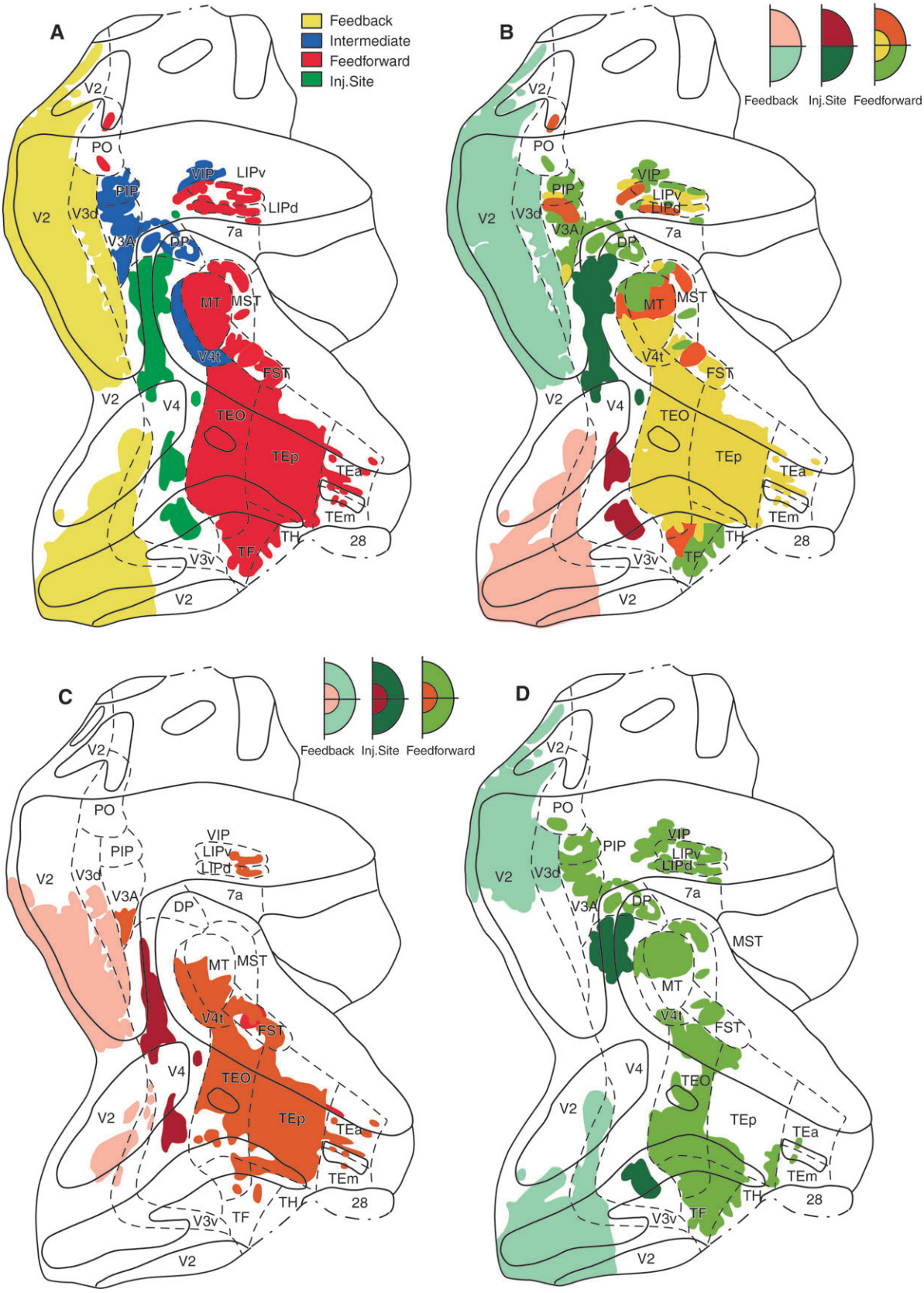

Figure 3. Distribution of connections of V4 with extrastriate cortex, shown on a 2-dimensional reconstruction of the cortex. (*A*) Total distribution of feedback, intermediate, and feedforward connections with V4. (*B*) Distribution of feedback connections with V4's upper and lower visual field representations, and of feedforward connections with V4's upper, lower, and central visual field representations. (*C*) Distribution of feedback and feedforward connections following injections into V4 sites representing approximately the central 5° of the visual field. (*D*) Distribution of feedback and feedforward connections following injections into V4 sites representing eccentricities beyond about 5°. For color-coding of data, see small inserts. For other conventions, see Figures 1 and 2.

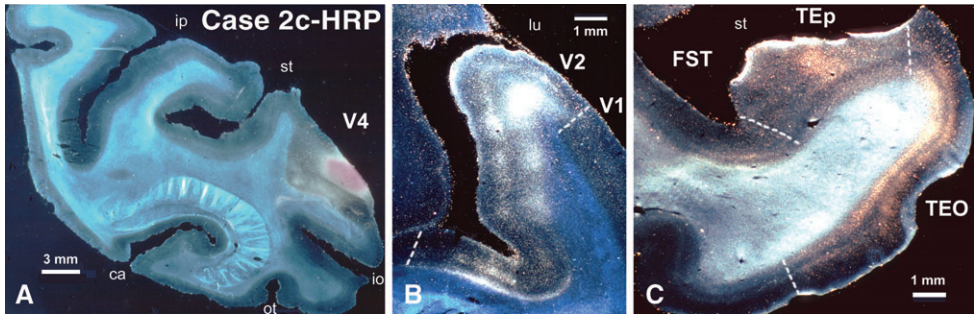

Figure 4. Photomicrographs of a representative case (Case 2c-HRP) illustrating the laminar distribution of cells and terminals following an injection into area V4. (*A*) The injection of HRP in V4 on the prelunate gyrus is shown on a coronal section. (*B*) Labeling posteriorly in V2 indicates feedback projections. (*C*) Labeling anteriorly in TEO and TEp indicates feedforward projections. See text for details.

V4 to V2 and V3 were located dorsally, consistent with the visual topography described for these 2 areas (Gattass et al. 1981, 1988; Burkhalter et al. 1986; Rosa et al. 1988). Anterior to V4, in areas V4t, TEO, TEp, TEm, TEa, and FST, there was widespread overlap in the projections from the central 5° of the upper and lower fields of V4 (see yellow zones in Fig. 3*B*) of V4, consistent with the increasing receptive field sizes of neurons in these areas as well as the expansion in the representation of their central visual fields (Gross et al. 1972; Desimone and Gross 1979; Maguire and Baizer 1984; Ungerleider and Desimone 1986; Fiorani et al. 1989; Boussaoud et al. 1991). There was also overlap in the projections from the upper and lower fields of V4 in areas MT, MST, FST, V3A, PIP, LIPd, and LIPv, and TF, but in these areas segregated inputs from the upper and lower visual fields of V4 were also found, consistent with reports that these areas, located in the STS, intraparietal sulcus, and parahippocampal gyrus, contain representations of both the upper and lower visual fields (Van Essen and Zeki 1978; Gattass and Gross 1981; Maunsell and Van Essen 1983c; Gattass et al. 1985; Ungerleider and Desimone 1986; Colby et al. 1988; Gattass et al. 1988; Andersen et al. 1990).

Connections with Central and Peripheral Field Representations in V4

Connections of the occipital, temporal, and parietal areas with the portions of V4 representing approximately the central 5° of the visual field and with those portions of V4 representing the periphery (eccentricities greater than about 5°) are summarized in Figure 3*C*,*D*, respectively. Posterior to V4, in areas V2 and V3, the projections were in topographic register with the portion of the visual field represented at the V4 injection sites. Central field representations in V4, located laterally in the cortex, projected to the central field representations in V2 and V3, also located laterally in the cortex. By contrast, peripheral field representation in V4, located more medially in the cortex, projected to the peripheral field representations in V2 and V3, also located more medially in the cortex. Other instances of topographically organized projections were also found, but at a much coarser level. For example, central representations in V4 tended to project to the more anterior portion of area MT, the more lateral portion of TEO and TEp, and the more anterior portion of V4t, whereas peripheral representations in V4 tended to project to the more posterior portion of area MT, the more medial portion of TEO and TEp, and the more posterior portion of V4t, which is consistent with the retinotopic mapping studies of these areas (Gattass and Gross 1981; Desimone and Ungerleider 1986; Boussaoud et al. 1991). Interestingly, for TEp, the central field inputs from V4 were far more extensive. By contrast, considerable overlap in the connections with the central and peripheral fields of V4 was found in parietal areas LIPd and LIPv and in parahippocampal area TF. However, in these areas, the peripheral field connections with V4 were more extensive. Finally, a number of areas were found to receive projections from peripheral but not central V4, and vice versa. Areas with only peripheral field connections included occipitoparietal areas DP, PIP, PO, and VIP, and superior temporal area MST, some of which are known to have an expanded peripheral field representation. Areas with only central field connections included superior temporal area FST and inferior temporal area TEa, both of which contain neurons whose receptive fields always include the center of gaze (Desimone and Gross 1979; Desimone and Ungerleider 1986).

Thus, in general, retinotopically organized visual areas had topographically organized connections with V4. Areas with coarser retinotopy had more coarse topographic connections. Of those areas with little or no retinotopy, such as those in parietal and temporal cortex, there was an asymmetry in the connections with V4, such that central visual field connections predominated with the inferior temporal cortex, whereas peripheral visual field connections predominated with the parietal and parahippocampal cortices.

Individual Cases

Below we describe the details of the connections of V4, using data from individual cases. The cases we illustrate were selected to emphasize the differences between connections from the central and peripheral field representations of V4, derived from anterograde and retrograde injections in this area.

Case 1

Case 1 received an injection of ^{3}H in the lower field of V4 at eccentricities spanning about 2–15° (Fig. 5 and Tables 1 and 2). This case was prepared in an attempt to obtain the entire projection field of dorsal V4. Case 1 revealed 1) feedback projections to V1 (not illustrated), V2, and V3, with the projections to V1 and V2 more restricted than the one to V3; 2) strong feedforward projections to TEO, TEp, and MT, but only sparse feedforward projections to LIPd and LIPv; and 3) intermediate-type projections to V3A and V4t (Table 2). Consistent with the injection site being centered near the vertical meridian of V4, the projections to V2 and MT were located at their posterior borders, where the vertical meridian is also represented.

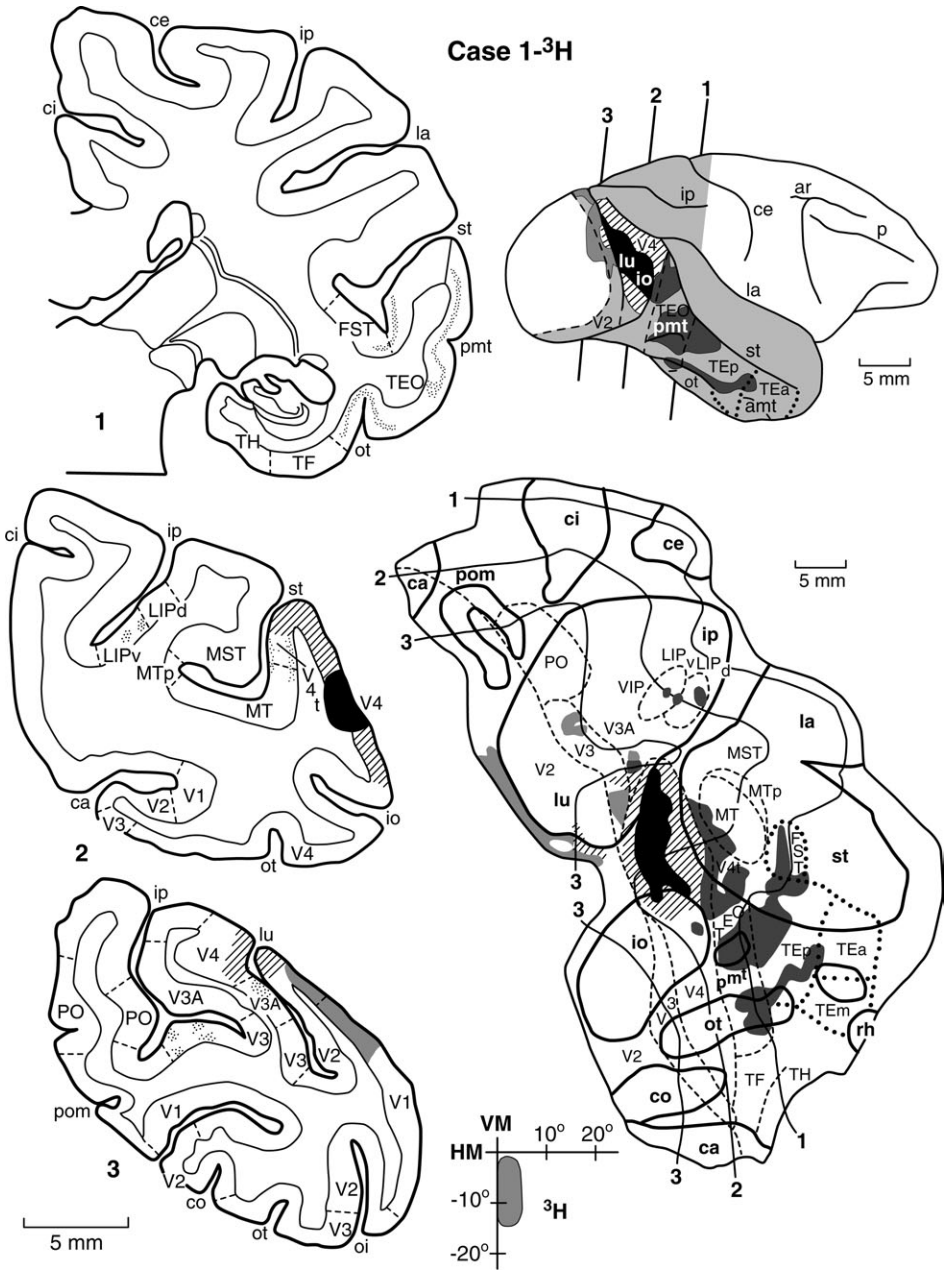

Figure 5. Case 1-^{3}H: Distribution of labeled terminals following injections of tritiated amino acids into the lower field representation of V4, shown on coronal sections at the levels indicated on the lateral view of the hemisphere (upper right) and on a 2-dimensional flattened map (lower right). The 2-dimensional map has been cut at the V1/V2 border. The thin lines running through the map indicate layer IV contour lines from the selected coronal sections (1–3). On the coronal sections, the injection site is shown in black, the dots indicate the relative density and laminar distribution of labeled terminals, and the dashed lines indicate the myeloarchitectonic borders of visual areas. On the lateral view of the hemisphere, the injection site is shown in black, the halo surrounding the injection site with stripes, projections including layer IV in dark gray, and projections excluding layer IV in light gray. The portion of the visual field corresponding to the back-transformation of the projection to V2 is shown in gray at bottom. Abbreviations: ce, central sulcus; ar, arcuate sulcus; p, principal sulcus. For other conventions, see Figures 1 and 2.

Case 2

Case 2 received an injection of HRP in the central portion of V4's lower visual field (Case 2c) at an eccentricity of 2° (Fig. 6), and an injection of ^{3}H in the peripheral portion of V4's lower visual field (Case 2p) at an eccentricity of 16° (Fig. 7). A comparison of Cases 2c and 2p revealed: 1) feedback projections to V1 (not shown), V2, and V3, with those from the central field representation of V4 located laterally and those from the peripheral field representation of V4 located dorsomedially; 2) a stronger feedforward projection to TEO from V4's central field representation than from its peripheral field representation, with the former located mainly laterally and the latter located mainly medially; 3) a stronger feedforward projection to TEp from V4's central field representation than from its peripheral field representation, with the former located throughout the area and the latter confined to its medial portion; 4) the presence of label in V3A (intermediate-type projection) and LIPd (feedforward projection) after the peripheral visual field injection but none after the central visual field injection; and 5) extremely sparse labeling of cells, but no terminals, in areas TF and TH after the central visual field injection only. Overall, for Case 2, the most prominent finding was the extensive labeling in

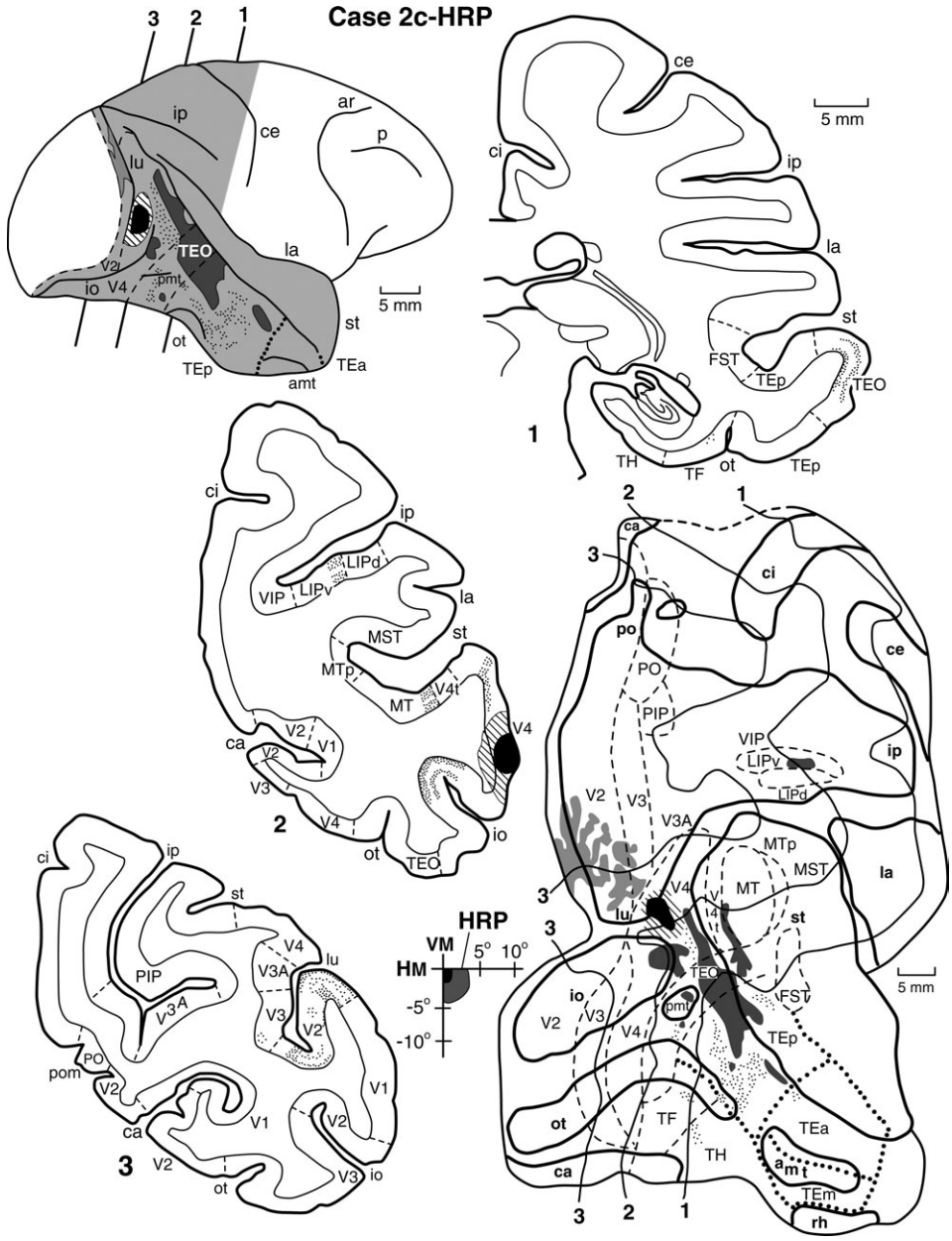

Figure 6. Case 2c-HRP: Distribution of labeled cells and terminals following an injection of HRP into the central lower field representation of V4. On the lateral view of the hemisphere and on the 2-dimensional map, labeling of both cells and terminals is shown in gray, whereas labeling of cells without terminals is shown as dots. The receptive field recorded at the injection site is shown in black and the portion of the visual field corresponding to the back-transformation of the projection to V2 are shown in gray at bottom. For other conventions, see Figures 1, 2, and 5.

the temporal lobe after the central field injection and the limited labeling after the peripheral field injection.

Case 3

Case 3 received an injection of ^{3}H in the central portion of V4's lower visual field (Case 3c) at an eccentricity of 3° (Fig. 8) and an injection of HRP in the peripheral portion of V4's lower visual field (Case 3p) at an eccentricity of 8° (Fig. 9). We prepared this case like Case 2, except that in this case we reversed the placement of the ^{3}H and HRP injections into V4's central and peripheral visual fields. Note that in Case 3 the receptive field recorded at the injection sites did not extend as far peripherally as our estimates based on the location of the feedback projections to V2 and V3. According to those estimates, the injection in Case 3c corresponded to eccentricities extending from 2° to 15° and the injection in Case 3p corresponded to eccentricities extending from 10° to 20°. A comparison of Cases 3c and 3p revealed 1) a feedback projection to V1 from the central field representation of V4 but not from V4's peripheral field representation (Tables 1 and 2); 2) a mixture of feedback and intermediate-type connections with V2 and V3, with those from the central field representation of V4 located laterally and those from the peripheral field representation of V4 located dorsomedially; 3) a mixture of intermediate-type and feedforward connections with MT, with those from the central field of V4 located more anteriorly than those from V4's periphery; 4) overlap in the feedforward projections to TEO from the central and peripheral field representations, with those from the former

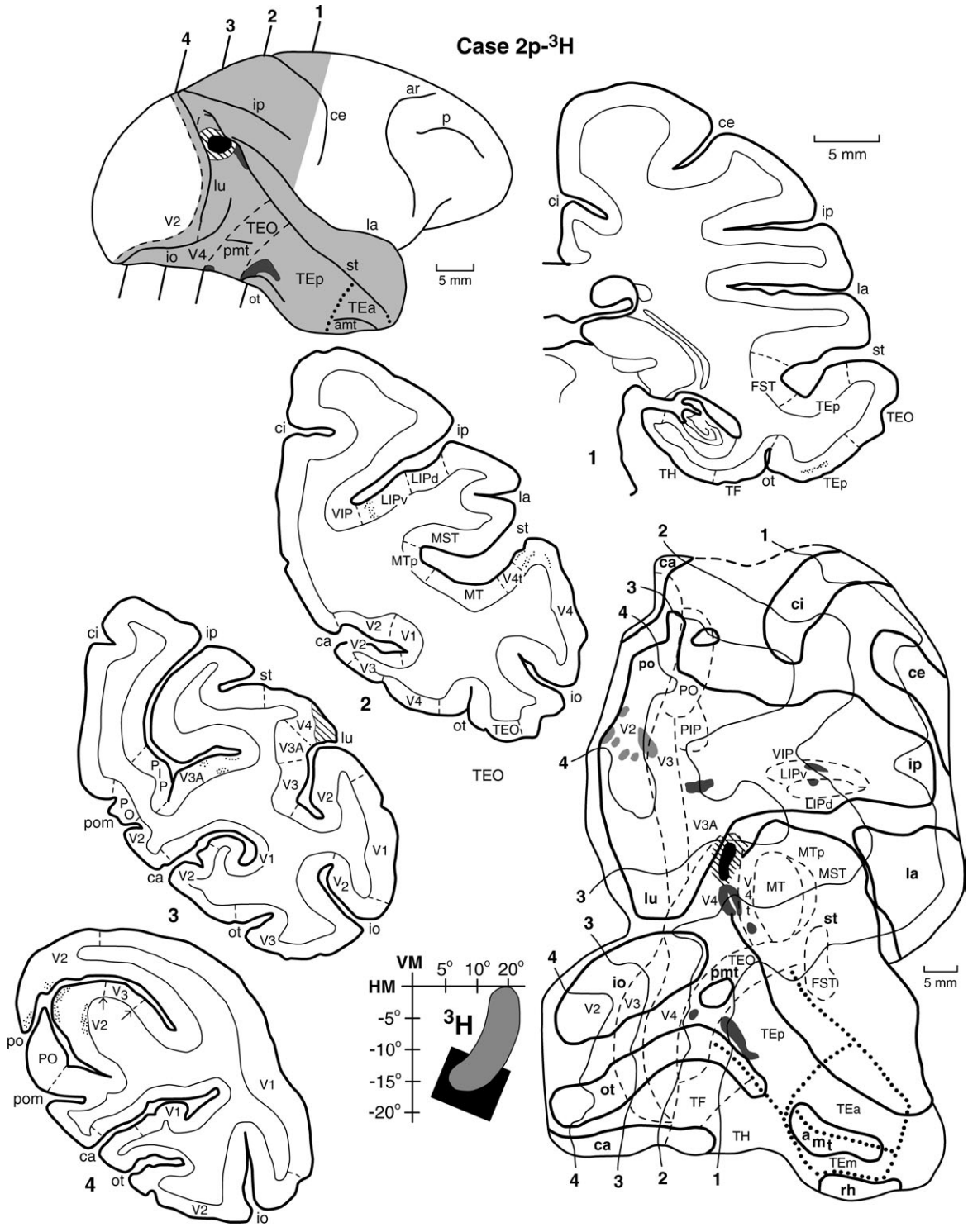

Figure 7. Cases 2p-^{3}H: Distribution of labeled terminals following an injection of tritiated amino acids into the peripheral lower field representation of V4. For conventions, see Figures 1, 2, 5, and 6.

being far more extensive; 5) considerable overlap in the feedforward projections to TEp and TF from the central and peripheral field representations of V4, with those from the former being somewhat more extensive; 6) the presence of label in V3A, DP, LIPd, FST, and area 7a after the peripheral visual field V4 injection but virtually none after the central visual field injection; and 7) a projection to the ventral portion of V4, close to its anterior border, after the peripheral field injection, suggesting that the injection site in dorsal V4 involved the representation of the horizontal meridian. Thus, for Case 3, the most prominent finding was the more widespread temporal lobe labeling after the central field injection and the more widespread occipitoparietal labeling after the peripheral field injection.

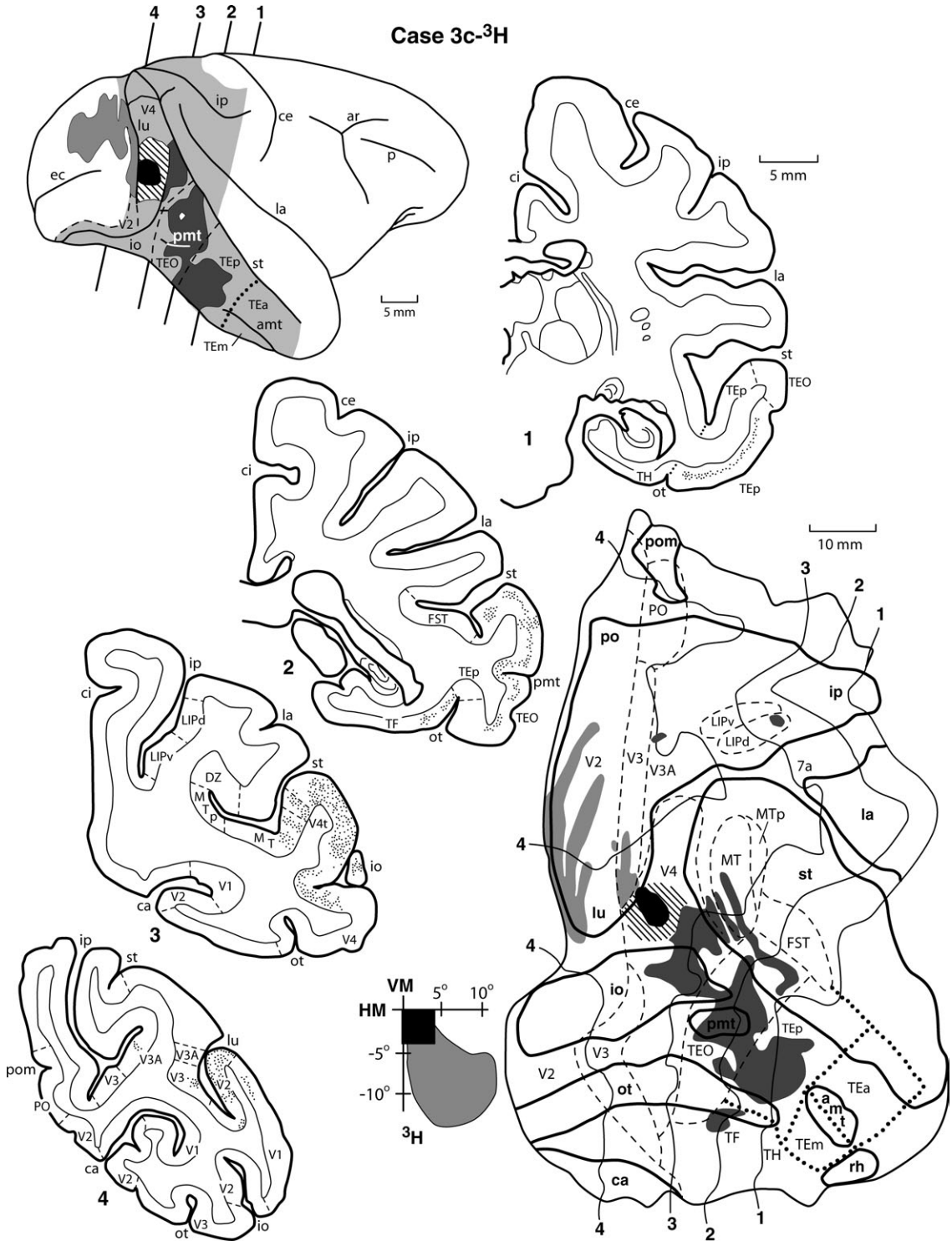

Figure 8. Case 3c-^{3}H: Distribution of labeled terminals following an injection of tritiated amino acids into the central lower field representation of V4. ec, external calcarine sulcus. For conventions, see Figures 1, 2, 5, and 6.

Case 4

Case 4 received injections of fluorescent dies in dorsal V4. An injection of FB was place in the central portion of V4's lower visual field (Case 4c) at an eccentricity of 2° (Fig. 10), and an injection of DY in the peripheral portion of V4's lower visual field (Case 4p) at an eccentricity of 18° (Fig. 11). In both cases, the receptive field recorded at the injection site did not extend as far peripherally as our estimates based on the location of the feedback projections to V2 and V3. According to those estimates, the injection in Case 4c corresponded to eccentricities extending from 1° to 7° and the injection in Case 4p corresponded to eccentricities extending from 18° to 35°. A comparison of Cases 4c and 4p revealed a very similar pattern of connections as the 2 previous cases: 1) feedforward projections

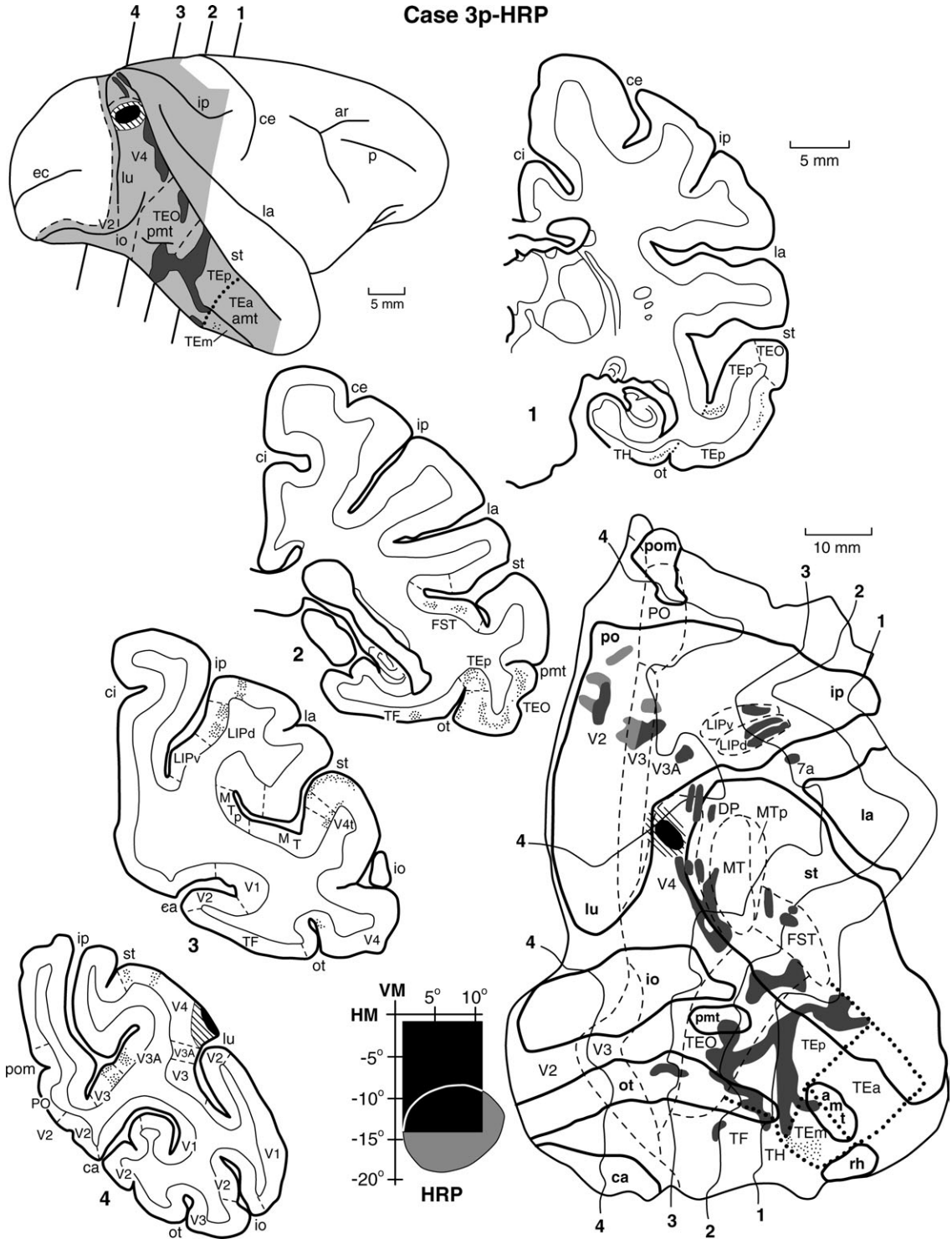

Figure 9. Cases 3p-HRP: Distribution of labeled cells and terminals following an injection of HRP into the peripheral lower field representation of V4. ec, external calcarine sulcus. For conventions, see Figures 1, 2, 5, and 6.

from V1 (see Tables 1 and 2), V2, and V3; 2) a stronger feedback projection from TEO and TEp to V4's central field representation than to its peripheral field representation; and 3) the presence of label in V3A (intermediate-type connection) and LIPd (feedback projection) after the peripheral visual field injection but not after the central visual field injection. Overall, for Case 4, the most prominent finding was the extensive labeling in the temporal cortex and the limited labeling in the occipitoparietal cortex after the central field injection compared with the peripheral field injection.

Cases 5c and 6p

Cases 5c and 6p received, respectively, an injection of HRP in the central portion of V4's upper visual field at an eccentricity of 4° (Fig. 12) and an injection of HRP in the peripheral portion of V4's upper visual field, at an eccentricity of 20° (Fig. 13). For the

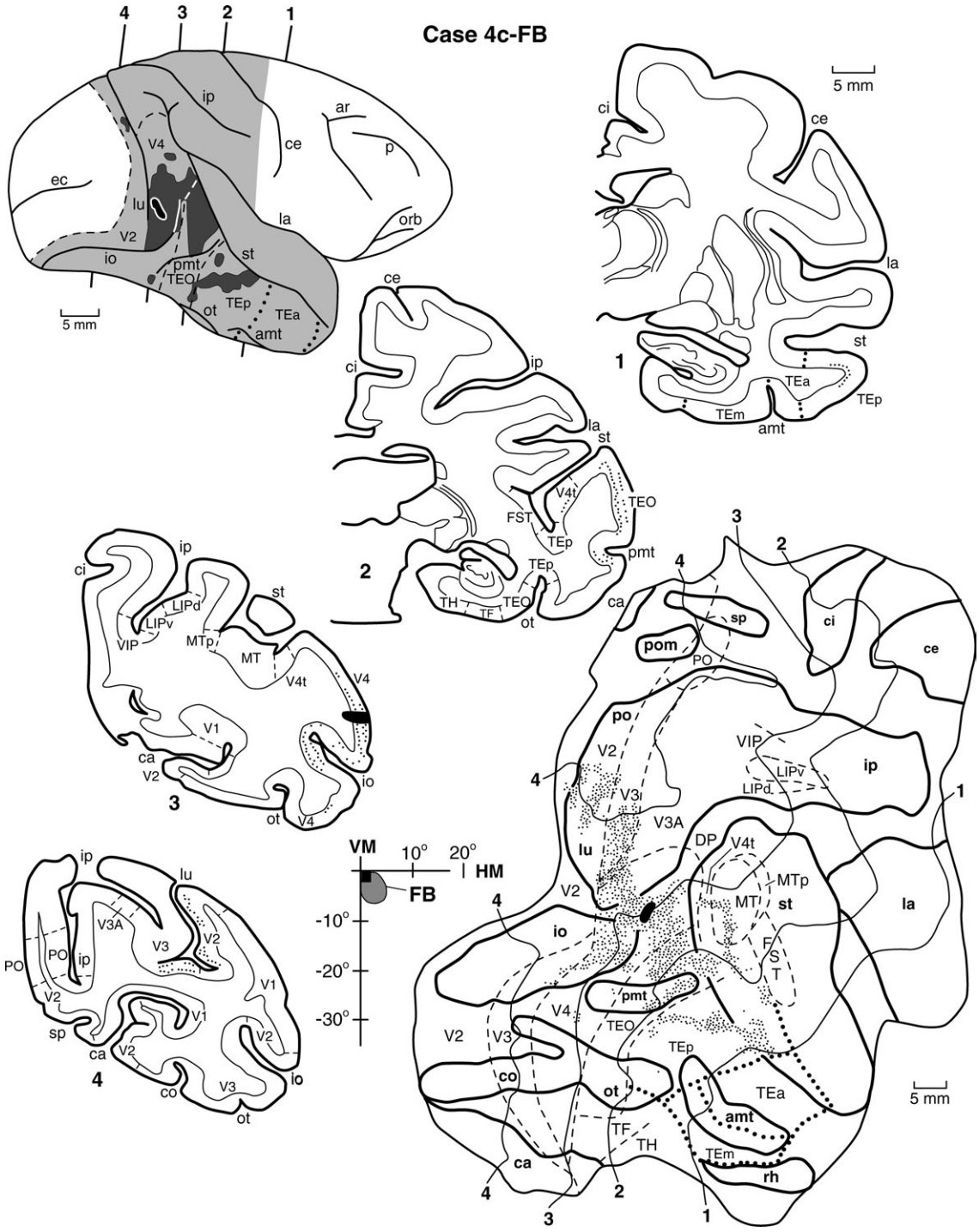

Figure 10. Case 4c-FB: Distribution of labeled cells following an injection of FB into the central lower field representation of V4. Labeled cells are shown as dots. Abbreviations: ec, external calcarine sulcus; orb, orbital sulcus. For conventions, see Figures 1, 2, 5, and 6.

latter case, only the labeled cells are plotted on the flattened maps because the terminal anterograde label was minimal. A comparison of Cases 5c and 6p revealed 1) topographically organized connections with V2 and V3, such that those with the central field representation of V4 were located laterally and those with the peripheral field representation of V4 were located ventromedially; 2) topographically organized connections, albeit on a coarser scale, with V4t and TEO, such that those with the central field representation of V4 were located more anteriorly in V4t and more laterally in TEO relative to those with the peripheral field representation of V4; 3) strong TEp connections with the central field representation of V4, but a paucity of such connections with the peripheral field representation of V4; and 4) the presence of label in V3A, PO, MST, VIP, and TF after the peripheral visual field injection but none after the central visual field injection. Thus, as in the lower field cases, in these 2 upper field cases, there was more widespread temporal lobe labeling after the central field injection and more widespread occipitoparietal and parahippocampal labeling after the peripheral field injection.

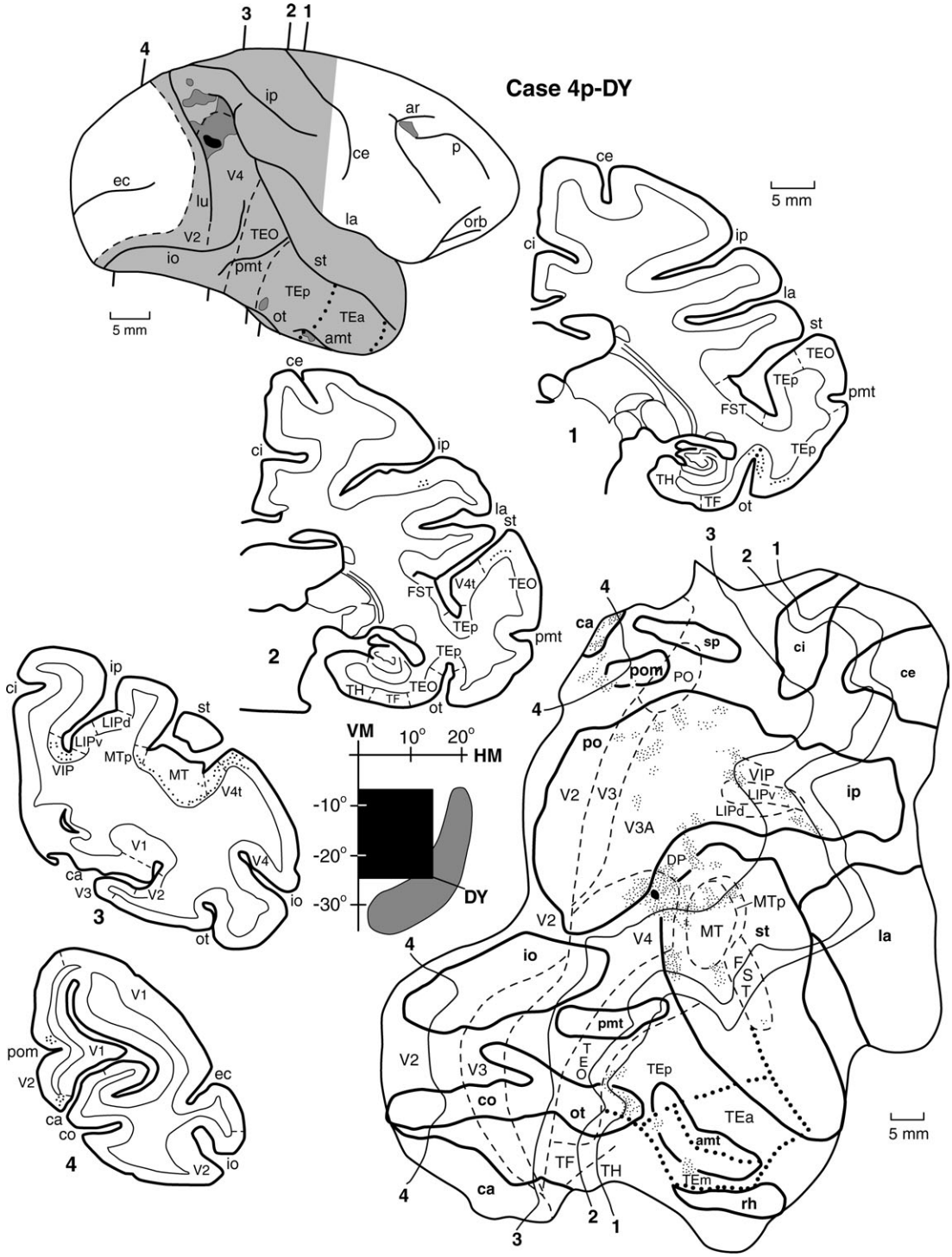

Figure 11. Case 4p-DY: Distribution of labeled cells following an injection of DY into the peripheral lower field representation of V4. Abbreviations: ec, external calcarine sulcus; orb, orbital sulcus. For conventions, see Figures 1, 2, 5, and 6.

Frontal Connections

Figure 14 summarizes the connections of V4 with the prefrontal cortex, as illustrated for 4 injections of the central lower field representation, one injection of the central upper field representation, 3 injections of the peripheral lower field representation, and one injection of the peripheral upper field representation. In these cases, the connections were with the arcuate sulcus and immediately adjacent portion of the prearcuate gyrus, namely, with the FEF. The results indicated a trend for the central field portions of V4 to be connected with the more posterior portion of the FEF (see dots in Fig. 14) and the peripheral field portions of V4 to be connected with the more anterior portions of the FEF (see exes in Fig. 14). Moreover, projections from the upper field of V4 tended to be located more ventrally in the FEF than those from the lower field of V4. This organization of the FEF is consistent with the ones proposed by

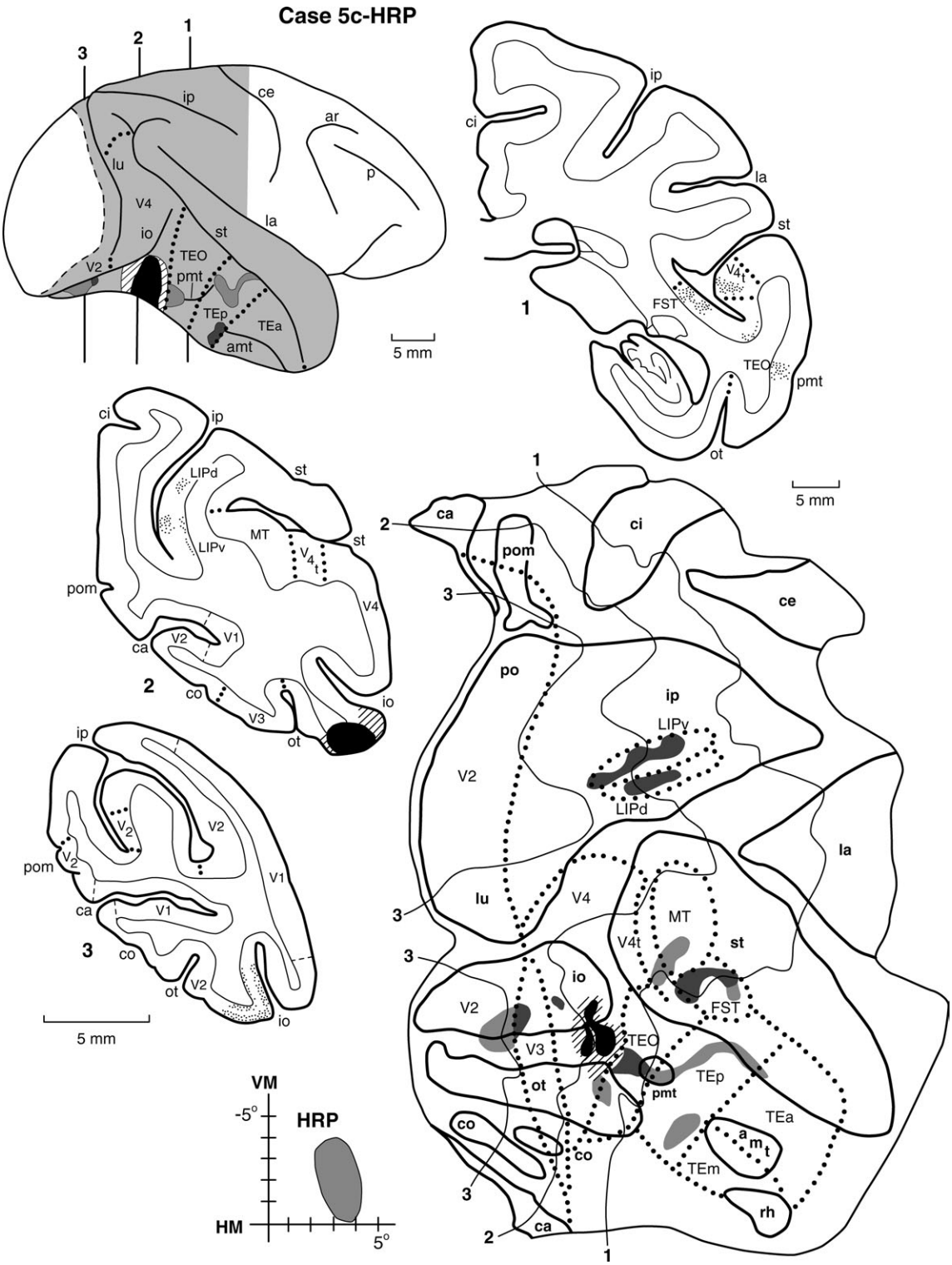

Figure 12. Case 5c-HRP: Distribution of labeled cells and terminals following an injection of HRP into the central upper field representation of V4. For conventions, see Figures 1, 2, 5, and 6.

Barbas and Mesulam (1981), Schall et al. (1995), and Stanton et al. (1995).

Discussion

In the present study, we examined the full set of inputs and outputs of area V4, based on injections of 21 anterograde and retrograde tracers placed into retinotopically specified locations in the area. Our results, summarized in Figure 15, demonstrated connections with occipital, temporal, parietal, and frontal regions. Importantly, we found an asymmetry in the connections with temporal and parietal cortex, with the central field representations of V4 having connections predominantly

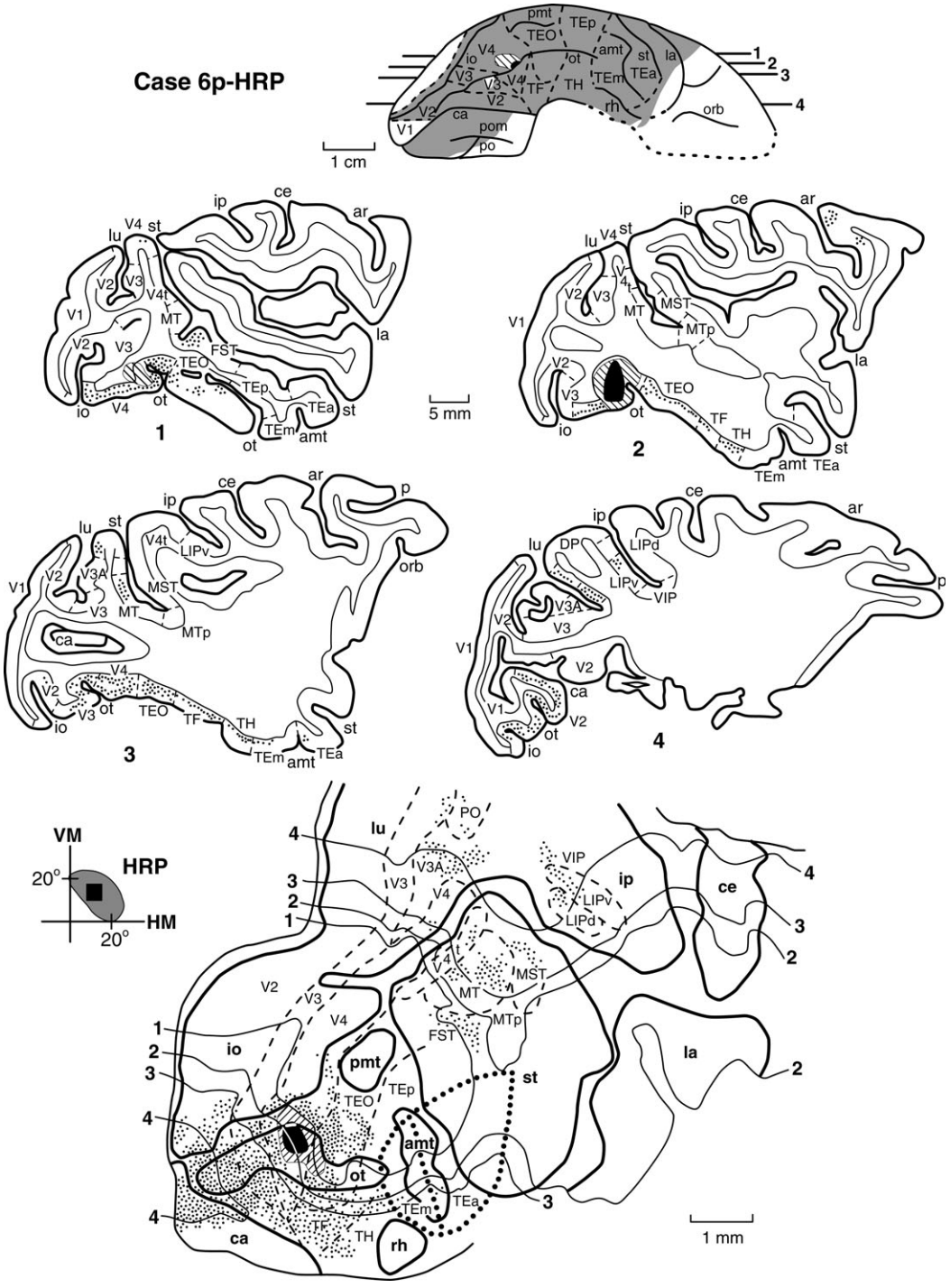

Figure 13. Case 6p-HRP: Distribution of labeled cells following an injection of HRP into the peripheral upper field representation of V4. orb, orbital sulcus. For conventions, see Figures 1, 2, 5, and 6.

with inferior temporal cortex and the peripheral field representations of V4 having connections predominantly with the occipitoparietal cortex. In the following sections, we discuss each of the regions connected with V4, and then consider the significance of V4's asymmetric projections to temporal and parietal cortices.

Connections with the Occipital Lobe

After injections in V4, dense labeling in occipital cortex appeared in V2 and V3. In general, these connections were topographically organized, although each injection site usually produced 2 or more patches of label in both areas. The distribution of cells in both V2 and V3 indicated feedforward inputs from these areas to V4. Projections from V2 to V4 have been found previously (Kuypers et al. 1965; Cragg and Ainsworth 1969; Zeki 1978; Rockland and Pandya 1981; Shipp and Zeki 1985; Zeki and Shipp 1989; Felleman, Xiao, et al. 1997; Gattass et al. 1997) as have those from V3 to V4 (Zeki 1978; Burkhalter et al. 1986; Felleman, Burkhalter, et al. 1997). Our results also indicated that the projections from V2 and V3 are

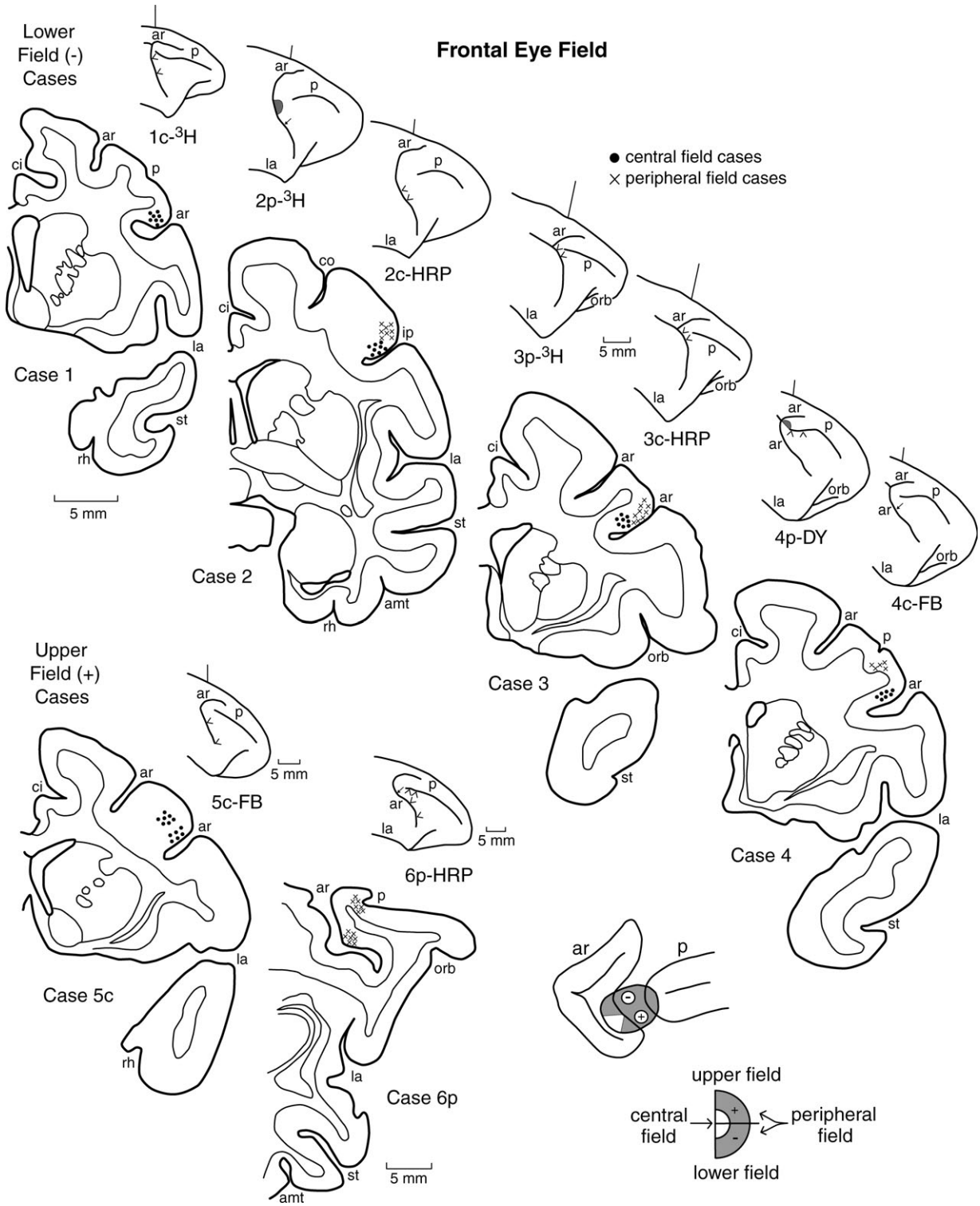

Figure 14. Distribution of labeled cells and terminals in frontal cortex following injections6 cases, shown on coronal sections at the levels indicated on the lateral view of the frontal lobe. Labeled cells and terminals following injections of V4's central visual field representation are shown as dots, whereas labeled cells and terminals following V4's peripheral field representations are shown as exes. A summary of the visual topography of the connections with the FEF is shown on a 2-dimensional map of the cortex at lower right. orb, orbital sulcus.

reciprocated by feedback projections to these areas from V4. The organization of the connections of V4 with V2 and V3 is in close correspondence with the visual field maps recorded in these areas (Gattass et al. 1981, 1988).

In addition to the cells in V2 and V3, labeled cells were also found in V1, but only after 3 of the 12 retrograde V4 injections. By contrast, labeled terminals were found in V1 after 6 of the 9 anterograde injections; the distribution of these terminals

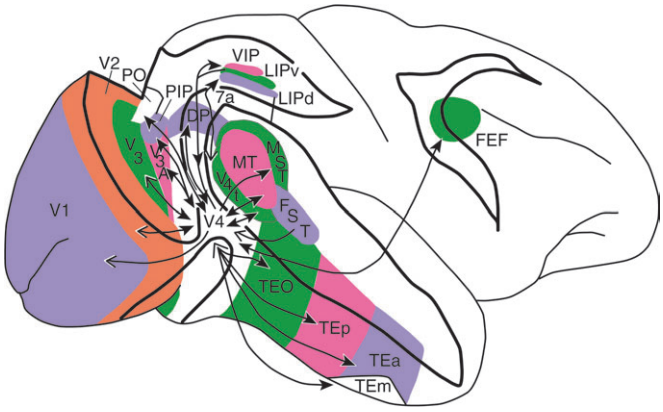

Figure 15. Summary illustrating the projections of V4 with other visual cortical areas, shown on a lateral view of the hemisphere with the sulci opened. Open arrowheads indicate feedback projections, closed arrowheads indicate feedforward projections, while projections of the intermediate type are illustrated with 2 closed arrowheads.

indicated a feedback projection from V4. A projection from V1 to V4 has been previously reported in cases with foveal V4 injection sites (Zeki 1978; Yukie and Iwai 1985; Nakamura et al. 1993) and it has also been shown that V4 projects back to V1 (Perkel et al. 1986; Sousa et al. 1991). Our data indicate that the projection from V1 to V4 includes eccentricities from the fovea to about 20°, and that the projection from V4 to V1 may be stronger than the projection from V1 to V4.

Reciprocal connections of V4 were also found with V3A, a finding not previously documented. Following injections in V4, labeled cells were found in both the superficial and deep layers of V3A and terminals were located in all layers, but were heaviest in layers I and VI. It therefore appears that the connection with V3A is of the intermediate type. V3A was first described by Van Essen and Zeki (1978) and was subsequently shown to contain both upper and lower field representations (Gattass et al. 1988). Consistent with this topography, we found label in V3A following both upper and lower visual field injections in V4, although the label was heavier after the latter. Unlike the projection from V1 to V3A, which appears to be confined to the peripheral field representation (Zeki 1980), we found that the projection from V4 to V3A included both central and peripheral field representations.

Connections with the STS

In the caudal STS, cells and terminals were found in areas V4t, MT, FST, and, in a few cases, MST. V4t is an area first described by Maguire and Baizer (1984), which borders V4 medially and MT laterally. Mapping studies have shown that it contains a representation of the lower visual field, with the central representation located ventral to the peripheral field representation (Desimone and Ungerleider 1986; Gattass et al. 1988; Fiorani et al. 1989). The location of labeled cells and terminals in V4t is consistent with this topography. Cells were located in both the superficial and deep layers and terminals were located in all layers, including layer IV but not heaviest in this layer. The connection between V4 and V4t therefore appears to be the intermediate type.

In all cases, moderate to heavy labeling was found in MT after V4 injections. Connections between MT and V4 have been described previously (Maunsell and Van Essen 1983c; Ungerleider and Desimone 1986). The locations of cells and terminals in MT varied considerably from case to case (see Table 2). In some cases, the cells were predominantly in the infragranular layers, but in other cases they seemed to be mainly in the supragranular layers; similarly, in some cases the terminals avoided layer IV, but in other cases they were heaviest in that layer. From our data, the overall impression was of a feedforward projection from V4 to MT, although the laminar distribution of labeling could support the prevailing view that V4 and MT have intermediate-type connections (Felleman and Van Essen 1991). The connections of V4 with MT followed the organization that has been described in mapping studies (Gattass and Gross 1981; Fiorani et al. 1989). Central field inputs from V4 projected ventrally within MT, whereas peripheral field inputs projected dorsally. Upper field inputs from V4 projected anteriorly within MT, whereas lower field inputs projected posteriorly.

Just anterior to MT in the fundus of the STS lies FST, an area with receptive fields that almost always include the center of gaze (Desimone and Ungerleider 1986). Consistent with this topography, V4 connections with FST were dominated by central visual field representations. Within FST, the cells showed a variable distribution; however, the terminals demonstrated mainly a feedforward projection from V4, in agreement with a prior finding that V4 receives a feedback projection from FST (Boussaoud et al. 1990).

Finally, after 3 tracer injections, HRP, FB, and ^{3}H, label was found in MST, an area lying medial to MT in the caudal STS (Maunsell and Van Essen 1983c; Desimone and Ungerleider 1986). In these cases, the connection was feedforward from V4 to MST. However, this connection should be considered a weak and inconsistent one, inasmuch it was not found in most of our cases and it was not reported previously in a study of the connections of MST (Boussaoud et al. 1990). The present study suggests that the connection may arise mainly from the far periphery of V4 (see Table 2).

It is interesting to consider the possible functionality of the connections of V4 with MT, FST, and MST, all of which contain many cells sensitive to direction of motion either in the frontal plane, in depth, or in both (Dubner and Zeki 1971; Bruce et al. 1981; Van Essen et al. 1981; Maunsell and Van Essen 1983a, 1983b; Albright 1984; Desimone and Ungerleider 1986; Saito et al. 1986; Tanaka et al. 1986). Cells in MT are also known to be sensitive to binocular disparity (Zeki 1974; Maunsell and Van Essen 1983b), and cells in MST appear to play a role in oculomotor control (Kamatsu and Wurtz 1988). It is possible that the connections of V4 with these motion-sensitive areas may contribute to the extraction of form from motion.

Connections with the Temporal Lobe

The injections in V4 resulted in cells and terminals located in both TEO (Boussaoud et al. 1991) and TE (von Bonin and Bailey 1947), and included TEp, located posteriorly, and TEm and TEa (Seltzer and Pandya 1978), located anteromedially and anterolaterally, respectively. Within TEO, the cells were located in both the superficial and deep layers, but the terminals were clearly indicative of a feedforward projection from V4 to TEO, in agreement with a prior study of the connections of TEO (Distler et al. 1993). Reciprocal connections between V4 and TEO have also been described in earlier studies (Ungerleider and Desimone 1986; Shiwa 1987; Morel and Bullier 1990), but there was only limited evidence that such connections are

topographically organized (Van Essen et al. 1991; Distler et al. 1993; see also, Weller and Steele 1992). In our study, the projections from V4 arose mainly from the central field representation; additionally, those from the central visual field of V4 were located lateral to those from V4's periphery. Of all areas connected with V4, TEO showed the strongest connection.

We also found that V4 is reciprocally connected with TE. There were strong connections with TEp, weaker connections with TEm, and even weaker, less reliable, connections with TEa. The projections to all subdivisions of TE were found to be feedforward. Connections of V4 with TE have been previously reported (Desimone et al. 1980; Shiwa 1987), although the projections in those earlier studies did not extend as far anteriorly in TE as in our study. We found a striking asymmetry in the projection from V4 to TE, such that V4's central field inputs to TEp were far more extensive than its peripheral field inputs, with the latter occupying the medial-most portion of the area. In addition, inputs to both TEm and TEa appeared to arise mainly from the central visual field of V4. The predominance of these central field inputs to TE is consistent with the fact that the receptive fields of neurons in this area almost always include the center of gaze (Gross et al. 1972; Desimone and Gross 1979).

Finally, we found connections between V4 and the parahippocampal gyrus in more than half the cases. There was a fairly reliable connection with TF, in particular the region of TF that has been termed "visually responsive TF," or VTF (visual portion of area TF) (Gattass et al. 1986; Boussaoud et al. 1991). Cells in TF were located in the infragranular layers, while terminals were heaviest in layer IV, indicating a feedforward projection from V4 to TF. Both central and peripheral field representations in V4 projected to TF, but the projection was mainly from V4's periphery. In addition, the projection to TF was from both the upper and lower fields in V4, consistent with the results from receptive field mapping in this part of TF (Boussaoud et al. 1991). In 3 of 21 cases only, we also observed a small projection anterior to TF, within TH, on the parahippocampal gyrus.

Connections with the Parietal Lobe

Injections in V4 produced label in the lower bank of the intraparietal sulcus, which includes 2 visual areas that have been termed the VIP (Maunsell and Van Essen 1983c; Ungerleider and Desimone 1986), and the LIP (Andersen et al. 1985, 1990). These 2 areas largely fall within cytoarchitectonically defined areas POai and POae of Seltzer and Pandya (1980), although some of the label was close enough to the cortical surface to be included in area 7a (Andersen et al. 1985; Cavada and Goldman-Rakic 1989). A projection from the prelunate portion of V4 to area LIP is well established (Seltzer and Pandya 1980; Rockland and Pandya 1981; Andersen et al. 1990), but the projection to VIP has not yet been reported. This projection, however, was not as robust as the projection to LIP. The connection with VIP appeared to be the intermediate type, whereas the one with LIP was feedforward from V4. For both VIP and LIP, the projection from V4 was predominantly from the peripheral field representation. Interestingly, direct projections from the peripheral field representation of V2 to both LIP and VIP have also been observed (Gattass et al. 1997).

More posteriorly in the parietal lobe, several other visual areas showed label, including DP, PIP, and PO. The connection with DP, an area located on the dorsal prelunate gyrus (Maguire and Baizer 1984), was of the intermediate type, and was limited to the periphery of V4's lower visual field representation. The connection with PIP, located in the lateral portion of the parieto-occipital sulcus (Colby et al. 1988), was also of the intermediate type. This connection was limited to the periphery of V4, but included both upper and lower field representations, consistent with the topography of PIP (Colby et al. 1988; see also Galletti et al. 1999). Finally, connections with PO, located in the medial portion of the parieto-occipital sulcus (Gattass et al. 1985; Colby et al. 1988; Galletti et al. 1999), were also observed. This connection, unlike the ones with DP and PIP, was of the feedforward type from V4. With the exception of one case, the projection to PO was with the periphery of V4, consistent with the overrepresentation of the periphery within this area (Gattass et al. 1985; Colby et al. 1988; Neuenschwander et al. 1994; Galletti et al. 1999) and confirming a prior report of a projection from the periphery of V4 to PO (Colby et al. 1988).

Connections with the Frontal Lobe

In the frontal lobe, cells were found in the inferior limb of the arcuate sulcus on its anterior bank, and, more sparsely, in the most posterior portion of the principal sulcus, a region termed the frontal eye field (FEF). Kuypers et al. (1965), Pandya and Kuypers (1969), and Barbas and Mesulam (1981) also demonstrated a projection from the prelunate gyrus to the cortex located between the inferior and superior rami of the arcuate sulcus in the frontal lobe. The projection in our study was located within cytoarchitectonic area FD, where retrograde (layers III and V) and anterograde (layers I–V, mainly in IV) labels were found, indicating an intermediate-type connection between V4 and the FEF. Connections with dorsal V4 were found in a more dorsal position within the FEF than were those found with ventral V4. Further, connections of the central field of V4 tended to be with the more posterior portion of the FEF than those of the peripheral field of V4, consistent with earlier proposals (Barbas and Mesulam 1981; Schall et al. 1995; Stanton et al. 1995). It has been shown that cells in the FEF have visual, saccade, and memory-related activity (Bizzi 1968; Mohler et al. 1973; Bruce and Goldberg 1985). Because this area, unlike other eye movement structures, has no direct connection to oculomotor muscles, V4 inputs as well as those from TEO (Distler et al. 1993) may provide visual information relevant for the programming of eye movements.

A Different Proposal for the Organization of the Macaque Prelunate Gyrus

There is considerable scatter in receptive field topography in area V4 (Desimone et al. 1984; Gattass et al. 1986, 1988; Tanaka et al. 1991) and connections between V4 and other visuotopically organized areas, such as V2, often show a patchy organization (DeYoe and Van Essen 1988; Yoshioka et al. 1992; Felleman, Xiao, et al. 1997; Xiao et al. 1999). Given the complexities in the anatomical connections, Zeki (1969) originally divided the prelunate gyrus into 2 areas (V4 and V4A), but later, based on physiological recordings, considered it to be comprised of several areas and termed the entire region the "V4 complex" (Van Essen and Zeki 1978; Zeki 1978). Consistent with the idea of a "complex," Stepniewska and Kaas (1996) have proposed that the macaque prelunate gyrus has 2 subdivisions, one caudal (DLc) and another rostral (DLr), based

largely on the pattern of connectivity with area V2. They found that single V2 injection sites may project to 2 or more patches in both subdivisions. They have suggested the name DL (or DL/V4) for area V4 based on similarities with area DL in the owl monkey.

The proposed visual topography of their DL is very similar to that described for V4 by Gattass et al. (1988; see also Gattass et al. 1997), with the foveal representations near to that in V2 and with the upper visual field represented ventrally and the lower visual field represented dorsally. However, their DL is somewhat smaller than our V4, and seems to extend less dorsally on the prelunate gyrus and less ventrally toward the occipitotemporal sulcus. Most recently, Stepniewska et al. (2005) have tested the proposed dorsal and ventral borders of DL/V4 by making injections of retrograde tracers into this area and adjacent regions. The injection sites were not placed under physiological control but were estimated to be inside or outside of V4/DL based on sulcal landmarks. They found that when their injections extended beyond the borders of V4/DL (estimated from surface views of a flattened cortex) they failed to find connections with V2, which would have been expected if the injection sites were in V4. They concluded that V4/DL is, indeed, somewhat smaller than found in the Gattass et al. (1988) mapping study. If so, this raises the possibility that some of our injections were placed outside V4.

In the present study, all of the V4 injections were placed under physiological control after receptive field mapping, and the resulting anatomical data are highly consistent with the visuotopic map of macaque V4 (Gattass et al. 1988), which has recently been confirmed in functional resonance imaging studies of macaque visual cortex (Brewer et al. 2002; Fize et al. 2003). Moreover, all of our injections resulted in label within V2, at the expected retinotopic location, which is the criterion used by Stepniewska et al. (2005) to define DL/V4. Further, had the peripheral field injections been at sites beyond V4, invading DP, label would have been observed on the medial surface of the hemisphere (Andersen et al. 1990; Stepniewska et al. 2005). This was not the case. Thus, we regard all our injections to be confined to V4.

We find it extremely difficult to make quantitative comparisons of areal boundaries based on qualitative comparisons of surface views; therefore, we have no reason to believe that there is any discrepancy across studies. We also have no anatomical data from our V4 injections supporting caudal and rostral subdivisions within V4; mapping data from macaque (Gattass et al. 1988; Brewer et al. 2002; Fize et al. 2003) and *Cebus* monkeys (Piñon et al. 1998) also do not provide support for such a distinction. However, the high receptive field scatter and the patchy anatomical connectivity with V2 may indeed allow for caudal and rostral functional subdivisions within V4, which may be resolved by future studies of neuronal properties in V4.

Comparison with Other Primates Species

Like V4 in macaque (Old World) monkeys, DL in New World monkeys transmits information from low-level visual areas in the occipital cortex to high-level visual areas in the temporal cortex (Weller and Kaas 1985, 1987; Cusick and Kaas 1988; Kaas and Krubitzer 1991; Steele et al. 1991; Weller et al. 1991; Weller and Steele 1992). It has therefore been proposed by several investigators that DL and V4 are homologous visual areas (Weller et al. 1991; Weller and Steele 1992). However, just as the definition of macaque V4 has evolved over the years (Zeki 1969, 1978; Van Essen and Zeki 1978; Gattass et al. 1988; Lyon and Kaas 2002; Stepniewska et al. 2005), so too has the definition of DL (Kaas 1997). Thus, it is extremely difficult to state definitively which region(s) in New World monkeys corresponds to V4 in macaques.

In their original pioneering mapping studies in *Aotus*, the owl monkey, Allman and Kaas (1974) defined DL as the area in dorsolateral cortex extending forward from the anterior border of V2 to the posterior border of MT. DL was similarly defined in *Saimiri*, the squirrel monkey, and in the marmoset monkey (Weller and Kaas 1987; Weller et al. 1991; Lyon and Kaas 2001). Subsequent studies subdivided this expanse of cortex into 2 or more areas. For example, Kaas and colleagues divided DL into caudal (DLc) and rostral (DLr) subdivisions based on patterns of connectivity in *Aotus* and *Saimiri* (Weller and Kaas 1987; Weller et al. 1991), and considered DLc to be homologous to V4 (Weller et al. 1991; Weller and Steele 1992). More recently, Kaas has acknowledged the existence of V3 posterior to DLc (Lyon and Kaas 2001). Based on electrophysiological recordings, Sereno and Allman (1991) and Sereno et al. (1994) described 3 areas located between V2 and MT in *Aotus*: posterior DL (DLp), intermediate DL (DLi), and anterior DL (DLa). DLp appears to correspond to V3 in macaques, DLi to V4 (as described here), and DLa to V4t (Sereno et al. 1994). DLi also appears to correspond to V4 in the *Cebus* monkey (Sousa et al. 1991; Piñon et al. 1998). Using electrophysiology, Rosa and Tweedale (2000) described 3 areas between V2 and MT in the marmoset monkey, termed VLP, VLA, and MTc; in this scheme, VLP may be equivalent to macaque V3, VLA to V4, and MTc to V4t (Rosa and Tweedale 2000). Thus, although the terminology of the visual areas and their precise borders may differ somewhat among the various studies, in both Old World and New World monkeys, there appear to be 3 separate visual areas located between V2 and MT.

Central versus Peripheral Visual Field Projections

V4 appears to play a major role in transmitting information forward from early visual cortical areas, in particular V2 and V3, to further stages of processing within the ventral stream for object recognition (Ungerleider and Mishkin 1982), including areas TEO and TE. Consistent with this role, neurons in V4 are sensitive to many visual features relevant to object perception, including color, spatial frequency, orientation, length, width, and curvature (e.g. Zeki 1980; Desimone and Schein 1987; Gallant et al. 1993, 1996; Youakim et al. 2001), and some have proposed functional modules within V4 (Yoshioka et al. 1992; Felleman, Xiao, et al. 1997; Xiao et al. 1999). In a prior study, we found that there are direct projections from V2 to TEO, bypassing V4, and we suggested that these bypass projections might provide a means for coarse-grained information to arrive rapidly in the temporal lobe (Nakamura et al. 1993). This advanced information about a stimulus might aid in constructing within area TE the initial representation of the overall shape and color of an object, with the fine-grained information arriving later to fill in the important details. It is therefore interesting to note that the connections of V4 are very similar to those of TEO (Distler et al. 1993; Webster et al. 1994). The exceptions are that, unlike V4, TEO projects to several areas located more anteriorly within the temporal lobe, including temporal polar area TG, perirhinal area 36, and area IPa within

the floor of the STS. Thus, at least for area TE, V4 and TEO appear to provide parallel sources of visual input.

V4 also appears to be an important source of visual information for several occipitoparietal areas within the dorsal processing stream (Ungerleider and Mishkin 1982), and thus may play an important and previously unrecognized role in visuospatial perception. V4 projections to occipitoparietal areas, including areas PIP, LIP, VIP, DP, and PO, were mainly from V4's peripheral field representations, consistent with findings from lesion studies in monkeys that the periphery makes a greater functional contribution to spatial vision compared with object vision (Mishkin and Ungerleider 1982).

Our findings are consistent with the accumulating evidence for differences in the cortical projections of central and peripheral visual field representations in extrastriate cortex. Zeki (1969) first noted that the foveal representation of V1, but not the remainder of the area, projects directly to V4, a finding replicated by Nakamura et al. (1993). Zeki (1980) also reported that the peripheral, but not central, representation of V1 projects to V3A (see also Ungerleider and Mishkin 1982), and Ungerleider and Desimone (1986) found that V3A receives a projection from the peripheral, but not central, representation of MT. In addition, it has been shown that the peripheral, but not central, representations of V1 and V2 provide direct inputs to PO (Colby et al. 1988). Finally, we previously reported that the peripheral, but not central, field representation of V2 projects to areas MST, LIP, VIP, and VTF (Gattass et al. 1997). The projections from the periphery of V4 to areas PIP, LIP, VIP, DP, and PO thus support the idea that V4, like earlier visual areas, provides direct peripheral field inputs to dorsal stream areas.

Differences between peripheral and central field inputs can be related, at least in part, to differences in the cortical magnification factor and/or to the extent of the visual field represented within an area (Gattass et al. 1997). In addition, as originally pointed out by Ungerleider (1985; see also DeYoe and Van Essen 1988; Desimone and Ungerleider 1989; Baizer et al. 1991), such differences may be related to the visual processing requirements of an area. Whereas ventral stream areas within occipitotemporal cortex receive preferential inputs from central field representations, consistent with the need for detailed form analysis for object vision (Ungerleider and Mishkin 1982), dorsal stream areas in occipitoparietal cortex receive preferential inputs from peripheral field representations, consistent with the role of these areas in spatial vision (Gattass et al. 1990). But what might be the significance of direct projections from the peripheral visual field of V4 to occipitoparietal areas? Earlier we proposed that, within the ventral stream, direct inputs from foveal V1 to V4, bypassing V2, and from V2 to TEO, bypassing V4, might provide a means for visual information to arrive rapidly in the temporal lobe (Nakamura et al. 1993). If so, then, by extension, the direct projections from the peripheral field of V4 to occipitoparietal areas could provide a direct route for information about the periphery to quickly reach parietal cortex and thereby rapidly activate circuits for spatial vision and spatial attention.

Notes

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Address correspondence to Dr Leslie G. Ungerleider, Laboratory of Brain and Cognition, NIMH, NIH, Building 10, Room 4C104, Bethesda, MD 20892-1366, USA. Email: ungerlel@mail.nih.gov.

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