Connections of the Dorsomedial Visual Area: Pathways for Early Integration of Dorsal and Ventral Streams in Extrastriate Cortex

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The dorsomedial area (DM), a subdivision of extrastriate cortex characterized by heavy myelination and relative emphasis on peripheral vision, remains the least understood of the main targets of striate cortex (V1) projections in primates. Here we placed retrograde tracer injections encompassing the full extent of this area in marmoset monkeys, and performed quantitative analyses of the numerical strengths and laminar patterns of its afferent connections. We found that feedforward projections from V1 and from the second visual area (V2) account for over half of the inputs to DM, and that the vast majority of the remaining connections come from other topographically organized visual cortices. Extrastriate projections to DM originate in approximately equal proportions from adjacent medial occipitoparietal areas, from the superior temporal motion-sensitive complex centered on the middle temporal area (MT), and from ventral stream-associated areas. Feedback from the posterior parietal cortex and other association areas accounts for <10% of the connections. These results do not support the hypothesis that DM is specifically associated with a medial subcircuit of the dorsal stream, important for visuomotor integration. Instead, they suggest an early-stage visual-processing node capable of contributing across cortical streams, much as V1 and V2 do. Thus, although DM may be important for providing visual inputs for guided body movements (which often depend on information contained in peripheral vision), this area is also likely to participate in other functions that require integration across wide expanses of visual space, such as perception of self-motion and contour completion.

Introduction

Influential models have proposed that visual processing takes place along parallel ventral and dorsal streams, which are seen as respectively emphasizing the processing of object identity versus object location and motion (Ungerleider and Mishkin, 1982), or conscious perception and analysis versus subconscious control of action (Goodale and Milner, 1992). While the “two streams” model remains a touchstone for the interpretation and integration of clinical, physiological, and anatomical data on visual processing, it continues to evolve. For example, several studies have suggested that the primate dorsal stream is, itself, formed by distinct dorsolateral and dorsomedial circuits, which mediate different aspects of visual behavior (Rosa and Tweedale, 2001; Galletti et al., 2003; Rizzolatti and Matelli, 2003). Perhaps reflecting this dual organization, anatomical studies have demonstrated parallel projections from the primary visual area (V1) to two heavily

myelinated, motion-sensitive dorsal areas, which in turn project to the posterior parietal cortex. One of these, the middle temporal area (MT) (Allman and Kaas, 1971), has become one of the most thoroughly investigated regions of the primate cortex. Consequently, we now know that MT is important for the perception of direction and speed of motion, as well as for motion awareness and computations that guide eye movements (Born and Bradley, 2005). In comparison, less attention has been directed to the other dorsal target of V1 projections, which in New World monkeys is named the dorsomedial area (DM) (Allman and Kaas, 1975). While several lines of evidence suggest that DM exists in other primates, including humans (Rosa and Tweedale, 2005; Pitzalis et al., 2006), determination of its exact homolog still requires additional study.

Clinical and experimental studies have demonstrated that areas located on the medial cortex near the occipitoparietal transition are important for “online” visual control of motor activity (Galletti et al., 2003; Gamberini et al., 2009). While it has been suggested that DM provides crucial inputs for this type of sensorimotor coordination (Rosa and Tweedale, 2001), there are good reasons to suspect that this area also contributes to other visual functions. For example, DM neurons display some of the sharpest orientation tuning found anywhere in the visual system, and their receptive fields have predominantly facilitatory surrounds; thus, maximal responses are observed when there is contour con-

Received Feb. 1, 2009; revised March 9, 2009; accepted March 12, 2009.

This work was funded by the Australian Research Council (Grants DP0451206 and LX0776009) and by the National Health and Medical Research Council (Grant 384115). Support from the University of Bologna's Institute of Advanced Studies is gratefully acknowledged. We thank Rita Collins and Katrina Worthy for the histological work.

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DOI:10.1523/JNEUROSCI.0529-09.2009

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Table 1. Summary of injections

Animal	Tracer and amount ^a	Visuotopic extent (eccentricity)	Laminar extent ^b	Area
CJ42 ^c	DY (crystal, 300 μ m)	Upper quadrant (2.5–7°)	C: layer 3 E: layers 1–5	DM
CJ52	FR (0.3 μ l)	Upper quadrant (6–15°)	C: layer 3 E: layers 1–5	DM
CJ36	FB (crystal, 450 μ m)	Upper + lower quadrants (4–18°)	C: layer 4 E: layers 2–6	DM
CJ35	FR (0.35 μ l)	Upper + lower quadrants (7–40°)	C: layer 4 E: layers 2–6	DM
CJ44	FB (crystal, 800 μ m)	Lower quadrant (3–10°) + Upper quadrant (10–50°)	C: layer 4 E: layers 1–6	DM
CJ52	FE (0.3 μ l)	Lower quadrant (6–18°)	C: layer 3 E: layers 3–5	DM
CJ49 ^c	FE (0.25 μ l)	Lower quadrant (10–35°)	C: layer 4 E: layers 3–5	DM
CJ25	FE (0.25 μ l)	Lower quadrant (18–80°)	C: layer 3 E: layers 2–6	DM, with PPM involvement
CJ44	DY (crystal, 800 μ m)	Upper + lower quadrants (7–55°)	C: layer 3 E: layers 1–4	MT

^aFor crystal deposits, the size is expressed as the maximum linear dimension measured parallel to the cortical layers in coronal or parasagittal sections.

^bC, Center of mass of the injection site. E, All layers encompassed by the injection site, determined across multiple sections.

^cCases for which full sets of electrophysiological data have been illustrated previously (Rosa et al., 2005).

tinuity between the receptive field and other parts of the scene (Baker et al., 1981; Lui et al., 2006). Moreover, neuromagnetic mapping in humans suggests that activity in the likely corresponding region reflects contour integration, in situations requiring comparisons across wide expanses of the visual field (Tanskanen et al., 2008). Thus, DM could also contribute to shape perception, a function traditionally linked to the ventral stream, when significant input from peripheral vision is required.

Understanding the nature of DM's contributions to visual cognition requires models based on its connections with other cortical areas, for which function is better established. Here we report on the connections of DM in marmosets, New World monkeys in which this area is easily accessible, and in which visual cortex has been mapped in detail. This has allowed the first quantitative analyses of the strengths, laminar patterns, and topographic organization of DM connections. These results shed light on a crucial aspect of the proposed subdivision of work within the dorsal stream, while demonstrating substrates for early-level interactions between the dorsal and ventral streams.

Materials and Methods

The welfare of the animals was monitored in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, with approval from Monash University and University of Queensland ethics committees. The main findings of the present report are based on the analysis of eight retrograde tracer injections performed in seven adult marmoset monkeys (*Callithrix jacchus*). These injections (Table 1) were selected for the present report primarily based on two criteria: there was no involvement of the white matter by the injection core, and the injection sites included the architecturally defined DM. Quantitative analyses were performed on the results of six injections, with two cases being included here solely for demonstration of aspects of topographic organization of the projections to DM. In one of these (CJ25-FE) the injection invaded the cortex anterior to DM, leading to labeling of additional connections. The other case (CJ44-FB) was excluded from quantitative analysis due to the placement of a large injection in MT of the same animal, which may have obscured cells projecting to DM.

Retrograde dye injections. The animals were premedicated with intramuscular injections of diazepam (3 mg $\cdot$ kg⁻¹) and atropine (0.2 mg $\cdot$ kg⁻¹) and anesthetized with ketamine (50 mg $\cdot$ kg⁻¹) and xylazine (3 mg $\cdot$ kg⁻¹). They were placed in a stereotaxic frame, and the occipital

cortex near the midline was exposed. Injection sites were chosen based on stereotaxic coordinates obtained in previous studies (Rosa and Schmid, 1995; Rosa and Elston, 1998). The retrograde fluorescent tracers diaminodino yellow (DY) and fast blue (FB) were directly applied into the cortex as crystals (~200 μ m in diameter) with the aid of blunt tungsten wires. As detailed in Table 1, these deposits resulted in injection sites several hundred micrometers in diameter, measured parallel to the cortical layers in histological sections. The dextran-conjugated tracers fluororuby (FR) and fluoroemerald (FE) were injected (0.2–0.4 μ l; 10% in saline) using 1 μ l microsyringes (Table 1), leading to smaller injection sites and fewer labeled cells. The exact location of the injection sites in relation to the borders of DM was assessed a posteriori, by histological examination (and, in several cases, by electrophysiological recordings; see below). The cortex was covered with gelfilm, the piece of bone removed during the craniotomy was fixed back in place with dental acrylic, and the wound was sutured. Antibiotics (Norocillin 0.1 ml, single dose) and analgesics (Carprofen 5 mg $\cdot$ kg⁻¹, s.c. for 2 consecutive days) were also administered.

Electrophysiological recordings. The animals were returned to their home cages for a period of 2 weeks, after which electrophysiological recordings were conducted in a terminal experiment. In four animals (cases CJ35, CJ36, CJ42, CJ49) the recordings were aimed at mapping the cortex around the injections sites, to assess the location of the injections relative to the putative boundaries of DM, while other cases were used for projects unrelated to the present report. The protocol for electrophysiological recordings has previously been described in detail (Bourne and Rosa, 2003). The animals were premedicated with intramuscular injections of diazepam (3 mg $\cdot$ kg⁻¹) and atropine (0.2 mg $\cdot$ kg⁻¹) and then anesthetized with ketamine (50 mg $\cdot$ kg⁻¹) and xylazine (3 mg $\cdot$ kg⁻¹). During the recordings, muscular paralysis and anesthesia were maintained by the intravenous infusion of pancuronium bromide (0.5 mg $\cdot$ kg⁻¹, followed by 0.1 mg $\cdot$ kg⁻¹ $\cdot$ h⁻¹) and sufentanil citrate (6–8 μ g $\cdot$ kg⁻¹ $\cdot$ h⁻¹). In addition, the animals were artificially ventilated with nitrous oxide/oxygen (7:3). Mydriasis and cycloplegia were induced by the topical application of atropine (1%) and phenylephrine hydrochloride (10%) eye drops. Contact lenses were used to bring into focus the surface of a 57 cm diameter translucent hemispheric screen centered on the eye contralateral to the cerebral hemisphere to be studied. After mapping the fovea of the contralateral eye using a reversible ophthalmoscope, the horizontal meridian of the visual field was defined as a line connecting the centers of the fovea and the blind spot (Troilo et al., 1993), and the vertical meridian as a perpendicular to the horizontal meridian through the center of the fovea. The doses of pancuronium used resulted in no

residual eye movements being detectable in these experiments, as evaluated by repeated mapping of the receptive field at the same recording site in foveal V1.

Parylene-coated tungsten microelectrodes were inserted in the vertical stereotaxic plane. The position of each electrode penetration was marked on digital images of the pattern of blood vessels on the cortical surface, obtained with a CCD camera during the surgery for tracer injection (Fig. 1). Recording sites were obtained at different depths in each penetration on the dorsal surface of the brain. Because these vertical penetrations entered the cortical surface at an acute angle, this often resulted in recording sites located in closely spaced ($<300\ \mu\text{m}$) columns (see Rosa et al., 2005). In addition, in some cases we made long penetrations along the midline cortex, where recordings were obtained every $400\text{--}500\ \mu\text{m}$. At each site the receptive fields of single units or small unit clusters were mapped by correlating changes in neural activity in response to the stimulation of specific portions of the visual field of the contralateral eye. A typical visual stimulus was a luminous bar ($2\text{--}20^\circ$ long, $0.2\text{--}1^\circ$ wide) moved or flashed (1 Hz) on the surface of the screen by means of a hand-held projector. The bar luminance was between 1 and $10\ \text{cd} \cdot \text{m}^{-2}$, on a $5 \times 10^{-2}\ \text{cd} \cdot \text{m}^{-2}$ background. Electrolytic lesions ($4\text{--}5\ \mu\text{A}$ for 10 s) were placed during the experiment to mark the transitions between areas, the end of electrode tracks, and sites of special interest.

An example of the electrophysiological determination of the injection site is shown in Figure 1. Recording sites in this animal (CJ35) indicated that the injection of FR was centered on a site representing the upper quadrant near the horizontal meridian, although with a likely slight invasion of the adjacent lower quadrant (receptive fields 12, 13, and 16). Confirming earlier reports (Rosa and Schmid, 1995) (see inset in Fig. 2 for summary), the data obtained in this animal demonstrate that the posterior boundary of DM, with the second visual area (V2), corresponds to the representation of the horizontal meridian (receptive fields 3 and 4). Furthermore, the representation of the lower quadrant on the exposed dorsal surface of DM (receptive fields 4–11) is located medial to the representation of the upper quadrant (receptive fields 13–17), and the vertical meridian representation forms the rostral boundary of this area (receptive fields 9 and 17). For each case for which this information was available, the receptive fields recorded closest to the injection sites ($<0.5\ \text{mm}$) are illustrated (see Figs. 5, 6, 8, 11). In addition to the data illustrated here, further electrophysiological recordings obtained in two of the present cases (CJ42 and CJ49) are available through an earlier publication (Rosa et al., 2005).

Perfusion, fixation, and tissue processing. At the end of the experiments the animals were deeply anesthetized with sodium pentobarbitone ($100\ \text{mg/kg}$, i.m.), and perfused transcardially with heparinized saline, followed by 4% paraformaldehyde in $0.1\ \text{M}$ phosphate buffer, pH 7.4. The brains were postfixed in the same medium for a minimum of 1 d before being cryoprotected by immersion in buffered paraformaldehyde solution containing increasing concentrations of sucrose. Frozen $40\text{--}\mu\text{m}$ -thick sections, following either the coronal (CJ42, CJ52) or the parasagittal (other cases) stereotaxic planes, were cut using a cryostat. A series of sections was mounted unstained on gelatinized slides for the analysis of cells labeled with fluorescent tracers, after quick dehydration in 100% ethanol, clearing in xylene, and coverslipping with DPX. Other series of sections were stained for Nissl substance, using cresyl violet, and for myelin, using either the Gallyas (1979) or the Schmued (1990) method. A

Figure 1. Results of electrophysiological recordings in animal CJ35, which received an injection of fluororuby in the location marked by the red "X". Top left, Digital image of the surface of the brain obtained before the injection (medial is toward the top, rostral to the right; scale bar, 1 mm). This image was used to guide electrophysiological recordings conducted 2 weeks later. The colored circles indicate the location of electrode penetration sites, where receptive fields were mapped (at depths between 600 and $800\ \mu\text{m}$), and the dashed lines indicate our estimates of the borders of the upper (DM+) and lower (DM-) quadrant representations in DM. In V2 (fields 1–3), the receptive fields migrate toward the horizontal meridian of the visual field, as the electrode is moved rostrally. Crossing into DM, the sequence reverts toward the vertical meridian (fields 4–9). Moving from medial to lateral within DM, the receptive fields move from the lower visual field (e.g., fields 8–11), across the horizontal meridian (field 12), into the upper visual field (fields 13–17).

final series of sections was stained free-floating for cytochrome oxidase activity (Wong-Riley, 1979), or, in one animal (CJ52), processed immunocytochemically to reveal the distribution of nonphosphorylated neurofilament (Bourne et al., 2007) [see Rosa et al. (2005), their Fig. 16, for illustrations of the staining pattern in this case].

Definition of extrastriate areas. Figure 2 (main panel) illustrates a summary of our current understanding of the subdivisions of the marmoset cortex. The homologies between areas of the marmoset visual cortex and those usually recognized in Old World monkeys have been summarized recently (Palmer and Rosa, 2006a), but will be mentioned briefly here where appropriate, to place our results in context. We have defined the boundaries of cortical fields projecting to DM based primarily on histological characteristics, guided by cytoarchitectural and myeloarchitectural criteria that have been previously validated against electrophysiological and connective data (Rosa et al., 1997, 2005; Rosa and Elston, 1998; Rosa and Tweedale, 2000; Burman et al., 2006, 2008; Palmer and Rosa, 2006a,b). While an extensive review of these criteria is beyond the scope of the present paper, here we summarize the cardinal features of several areas that are key to the interpretation of our results.

As shown in Figure 3 (top panel), area DM is defined by its dense myelination and by its broad bands of Baillarger, which are separated by a subtle, slightly less myelinated gap. This architectural field precisely coincides with a complete second-order representation of the visual field (Allman and Kaas, 1975; Rosa and Schmid, 1995). In DM thick radial fibers, which run from the white matter to the top of layer 3, crisscross with dense plexuses of tangential fibers, particularly at the levels of the inner and outer bands of Baillarger (Rosa et al., 2005). In addition, the inner band merges with the white matter without a noticeable gap. The overall effect is a matted appearance in low-power views (Fig. 3). These architectural criteria allow the definition of the borders of DM with all

Figure 2. Main panel, Summary of current knowledge of the cortical organization in the marmoset, a New World monkey. "Unfolded" representation prepared using the technique of Van Essen and Maunsell (1980). Discontinuities in the representation, introduced to minimize distortion, are indicated by the arrows. The red, blue, and green asterisks represent corresponding points on two sides of a discontinuity. Continuous gray lines indicate the main cortical folds, including the lips and fundi of the lateral and calcarine sulci, the fundi of the superior temporal and intraparietal dimples, and the limits of the medial, ventral, and orbital surfaces. The inset on the lower left shows a lateral view of the intact marmoset brain, with boundaries of some visual areas indicated to help orientation. Colors indicate visual areas, with continuous outlines indicating borders that have been characterized in detail, and dotted lines indicating borders that are based on histology only. The topographic organization of visual areas is indicated according to the following symbols: black squares, representations of the vertical meridian; white circles, representations of the horizontal meridian; "+", representations of upper quadrant; "−", representations of the lower quadrant. Borders of nonvisual areas that are relevant for the present study are indicated by dotted outlines (primary sensory fields in dark gray), and the approximate location of other fields is indicated by their acronyms or numerical designations for orientation purposes only (for details, see Burman et al., 2006, 2008; Burman and Rosa, 2009). aud, Auditory belt and parabelt areas; ER, entorhinal cortex; Ins, insular cortex; PR, parietal rostral area; PV, parietal ventral area; som, caudal somatosensory areas; STP, superior temporal polysensory cortex. Upper left, Magnified view of the dorsomedial area, showing its visuotopic organization as mapped by Rosa and Schmid (1995). The lower quadrant, together with the entire periphery of the visual field, forms a continuous map in the medial portion of DM. A complementary sector of the visual field including the central part of the upper quadrant plus most of the upper vertical meridian, is "detached" from this map, being represented in the lateral part of DM. The blue stars indicate the line of visual field discontinuity in a typical animal (see Rosa et al., 2005 for details).

adjacent areas. In area V2, which is located immediately caudal to DM, the bands of Baillarger area appear entirely fused, with the entire cortex between layers 3 and 6 appearing homogeneous (Fig. 3). While showing variations in density of myelination, the V2 cortex is not as darkly stained as DM (see also Rosa et al., 1997). Medially, a marked drop in myelin content marks the boundary of DM with the medial subdivision of cytoarchitectural area 19 (field 19m) (Fig. 3, top) [see also Palmer and Rosa (2006b)]. Finally, the cortex lateral and anterior to DM is relatively densely myelinated, but shows inner and outer bands of Baillarger that are more clearly separated from each other, and from the white matter. As reported by Rosa and Schmid (1995), this region contains a complex pattern of visual field representations, including the dorsointermediate field (DI), which appears in Figure 3.

Also visible in Figure 3 are portions of other topographically organized areas that form projections to DM. These include, in the top panel, the ventrolateral posterior (VLP) and ventrolateral anterior (VLA) areas, which form successive belt-like representations of the visual field on the lateral and tentorial surfaces of the occipital lobe (Fig. 2). Area VLA is moderately to lightly myelinated, and is characterized by sharply defined bands of Baillarger, which are separated from each other and from the

white matter by well defined, lightly stained gaps. Area VLP is less distinctly laminated, having transitional characteristics between V2 and VLA with respect to both density of myelination and separation of the bands of Baillarger. In the more anterior section shown in the lower panel of Figure 3, portions of the densely myelinated areas MT and MST [medial superior temporal; defined in the marmoset by Krubitzer and Kaas (1990)] are also illustrated.

The interpretation of the current results also required definition of posterior parietal fields, which to date remains a poorly understood aspect of New World monkey cortical organization. Here, the definition of fields was primarily histological. As in a previous study (Palmer and Rosa, 2006a), we recognized two primary architectural subdivisions, referred to as the dorsal and ventral subdivisions of the posterior parietal cortex (PPd and PPv). Field PPd is characterized by larger pyramidal neurons in layer 5 and more robust myelination, in comparison with PPv. The architectural characteristics and patterns of connections with premotor cortex suggest that PPd encompasses the likely homologs of fields Péc, MIP, LIP, and VIP of the macaque, while PPv includes fields Opt, PG, PF, and TPt (Bourne et al., 2007; Burman et al., 2008) (Fig. 2). Indeed, as illustrated in Figure 3 (bottom panel), the most lateral portion of PPd is occupied by a heavily myelinated region, which has the histological characteristics of the Old World monkey lateral intraparietal area (LIP) (Blatt et al., 1990). In addition, the putative LIP is typically separated from the main body of PPd by a narrow, less myelinated region, which is likely to correspond to the ventral intraparietal area (VIP). Likewise, PPv shows regional variations in its pattern of myelination, such as the distinction between fields PF and TPt shown in Figure 2. While the main fields PPd and PPv could be reliably defined in each animal, a precise delimitation of their finer subdivisions was more stringently dependent on the quality of the staining in the particular sections. Thus, we have chosen to anchor our quantitative analyses on the PPd/PPv distinction, while highlighting specific subfields where appropriate in the description of the results.

The interpretation of architectural patterns often results in uncertainty zones between areas (Fig. 3), which arise from various methodological factors. These include the different features revealed by different staining methods, the slightly different boundary locations in adjacent sections stained with different techniques, and the interference of localized histological artifacts (Burman and Rosa, 2009). These various sources of error resulted in what we considered, for the purposes of the present analysis, transition zones. For quantitative analyses, cells within the transition zones between architectural fields were assigned to one of two adjacent areas by bisecting these zones into equal halves (e.g., arrows in Fig. 3; lines in Fig. 4).

Documentation of results and analysis. Every section in the series used for analysis of fluorescent tracers was scanned in its entirety, using a Zeiss Axioplan 2 epifluorescence microscope equipped with a 20× dry objective. The location of each labeled neuron was mapped with a digitizing system (MD Plot3, Accustage). Photographs were obtained through Zeiss Pan-Neofluar objectives, and acquired as digital images using a Zeiss AxioCam and AxioVision v4.2 software (Carl Zeiss Vision).

Two-dimensional reconstructions of the cortical surface were obtained by graphically "unfolding" contours of layer IV of sections 400 μm

Figure 3. Myeloarchitectural characteristics of cortical areas of the marmoset (Gallyas stain). Transition zones between areas are indicated by lines overlying the cortex, and their centers by overlying arrows. In the lower panel, the extent of the main subdivisions of the posterior parietal cortex (PPd and PPv) is indicated by the arrowheads underlying layer 6. As discussed in Materials and Methods, these contain multiple subfields (including MDP, PEc, VIP, LIP, PF, and TPt, which are visible in this illustration).

apart, in such a way as to keep the neighborhood relationships between and within sections. For ease of comparison with previously published data in other species, these maps were prepared in the standard format proposed by Van Essen and Maunsell (1980), in which a discontinuity is introduced along the perimeter of area V1, thus making this area appear as a detached ovoid (to the left of right-hemisphere reconstructions). However, as indicated in Figure 2, to minimize angular distortions we have introduced additional discontinuities at reproducible locations (the dorsal and ventral limits of the frontal lobe midline, and the temporal pole); these were found to be necessary given the higher intrinsic curvature of the small brain of the marmoset, in comparison with that of the macaque.

Maps of the density of labeled cells were prepared by projecting the location of each labeled neuron or neuron cluster to the nearest location in layer 4, based on three-dimensional graphic reconstructions of this layer across serial sections. After these locations were transferred to two-dimensional maps, the relative density of labeled cells in different regions was calculated according to a square grid (400 μm side) superimposed on these maps; typically, given the spacing of sections, each grid subdivision typically included information from parts of 2 adjacent plotted sections. Because the number of labeled cells varies according to the size and type of injection, densities were expressed as a fraction of the maximum cell count observed in that particular case, which usually was observed in the

immediate neighborhood of the injection site (intrinsic connections). The locations of the injection sites, electrode tracks, and architectural transitions were also projected onto these maps, allowing correlation between different sets of data. To illustrate this approach, Figure 4 illustrates parasagittal sections from animal CJ35, together with an indication of how these planes of section projected into the unfolded reconstruction of this brain. Even a qualitative comparison reveals that regional variations in the density of labeled cells observed in these sections are reflected in the two-dimensional connection density map of this case (see Fig. 5). For example, the highest density of labeled cells (red) corresponds to the region immediately around the injection site (Fig. 4, section D), with distinct regions of relatively dense connections (orange, yellow) being found in the ventral and dorsal banks of the calcarine sulcus (sections D, E) and in ventral V2 (section D). Finally, variations in the density of label in area MT and the adjacent middle temporal crescent (MTc) can be correlated with the distribution observed in section A, which was cut nearly tangential to these areas.

Laminar patterns of connections were quantified using the proportion of labeled cells located in the supragranular layers, relative to the total number of labeled cells in a given area (%SLN) (Barone et al., 2000). Classification of the projections as being of a predominantly feedforward, intermediate (lateral), or feedback nature (Maunsell and Van Essen, 1983) used, as a first approximation, the criteria defined by Grant and Hilgetag (2005) for the cat visual cortex. Thus, projections characterized by %SLN values between 0 and 33 were classified as being feedback, those with values between 39 and 69 as lateral, and those with values >76 as feedforward; projections showing %SLN values between these bands cannot be unambiguously assigned to one of two adjacent categories. In area V1, we have considered the granular layer to correspond to Brodmann's layer IVc, given that this is the most likely homolog of layer 4 in other areas (for details, see Casagrande and Kaas, 1994). According to the nomenclature proposed by these authors, the sublayer of V1 that forms the main projection to areas DM and MT (Brodmann's layer IVb) is considered to represent deep layer 3 (layer 3c) [see also vogt Weisenhorn et al. (1995) and supplemental Fig. 1 (available at www.jneurosci.org as supplemental material)].

Estimation of the extent of the injection sites. The extents of DY and FB injection sites were estimated according to the criteria defined by Condé (1987). In Figures 6, 8, and 9, these injection sites appear as two concentric zones: a black region, indicating the combined extent of Condé's zones 0 and 1 (hence corresponding to a generous estimate of the tracer uptake zone), and a white region, corresponding to zones 2 and 3 (where the cytoarchitecture was disrupted, but no tracer uptake was expected). In illustrations of FR and FE injections (see Figs. 5, 7, 10–12) the black region indicates cortex containing fluorescent dye in the extracellular space (which is limited to the neighborhood of the needle track; Schmued et al., 1990), and the white region indicates the surrounding zone where virtually every cell body was brightly labeled. The involvement of different cortical layers, estimated in Nissl-stained sections, is summarized in Table 1.

We determined the portion of the visual field represented within the effective injection sites by analyzing the location of retrogradely labeled neurons in V1. To accomplish this, we plotted estimates of the isoeccentricity and isopolar lines in the reconstructed V1 of each animal, based on the function relating cortical magnification factor (CMF) to eccentricity (ecc) in the marmoset [$\text{CMF} = 3.95(\text{ecc} + 0.64)^{0.98}$ (Rosa et al., 2000a)]. Estimates for individual cases were linearly scaled so that the long axis of V1, measured in the bidimensional reconstructions, matched the length of the representation of the horizontal meridian as predicted by the magnification factor function. Given that the topographic organization of V1 in the marmoset is highly consistent between cases (Fritsches and Rosa, 1996), this procedure results in estimates that are correct within 10% of the eccentricity actually observed in electrophysiological recordings in the same animals [see Palmer and Rosa (2006b) for examples of this technique applied to the analysis of MT connections]. These estimates included but, in many cases, extended considerably beyond the extents of the excitatory receptive fields of cells recorded near the injection sites, perhaps reflecting projections that contribute to "silent" receptive field surrounds (Angelucci et al., 2002) and those involved

Figure 4. Series of parasagittal sections (A–F) showing the location of FR-labeled neurons (red) in case CJ35-FR (rostral to the right). The centers of the transition zones between areas are indicated by blue lines across the cortex. The levels of these sections are indicated in the inset (upper left), which is a two-dimensional reconstruction of the cortex in this case, prepared using the conventions shown in Figure 2. The locations of a few cortical areas [V1, V2, DM, MT, and the primary somatosensory area (S1)] are indicated in gray for orientation. The detailed map of distribution of label in this case is illustrated in Figure 5. Scale bars, 1 mm. Abbreviations for subcortical structures are as follows: Cel/CeM, central lateral/central medial thalamic nuclei; Cla, claustrum; Pul, pulvinar complex.

in establishing continuity across the visual field in areas that form second-order representations (Jeffs et al., 2009).

Results

Our study was designed with several specific aims. At the most basic level, we were interested in defining the relative contributions of different areas, and cortical streams, to the pattern of DM afferents. In addition, we were interested in establishing the hierarchical level of DM relative to other visual areas, based on the relative proportions of feedforward and feedback afferents, and in comparing the connections of DM with those of areas located rostral to dorsal V2 in Old World monkeys, to make informed inferences about the homologies across primate species. With these aims in mind, we placed injections at sites that collectively encompassed the entire territory of architecturally defined DM, and analyzed the data according to the relative numerical strength and laminar bias (%SLN) of the different projections. These quantitative analyses, combined with the topographic distribution of labeled cells, also allowed a test of whether or not the entire extent of DM receives a similar set of connections from

other visual areas, which is an important, but rarely performed check of the validity of the boundaries of proposed cortical areas.

The quantitative analyses reported below refer only to the extrinsic connections of DM. In the immediate neighborhood of the injection sites, we found it difficult to distinguish cells that were labeled by retrograde transport from those that incorporated the tracer passively by diffusion. Thus, the label densities within DM illustrated in Figures 5–13 need to be seen as minimum estimates, reflecting the adoption of what was probably an overly conservative criterion.

Areal and topographic distribution of labeled cells

The parasagittal sections illustrated in Figure 4 summarize the typical distribution of labeled neurons after injections in DM, which (as demonstrated below) was highly stereotyped among our cases. By far the highest concentrations of label were found in V1 (sections B–F) and V2 (sections D–F). Relatively dense projections also originated in MT and the surrounding middle temporal crescent area (MTc; see section A), in the occipitoparietal transition cortex, located immediately rostral to DM (dorsoanterior and dorsointermediate areas; DA and DI, shown in sections C–E), and in the ventrolateral areas VLA and VLP (sections A–D). In addition, this case (which involved the peripheral upper quadrant representation, as demonstrated in Fig. 1) showed a robust projection from the medial cortex ventral to DM (field 19m, in section F). Parietal projections to DM were densest from the dorsal subdivision of the posterior parietal cortex, with distinct foci of labeled neurons present in a rostral region, which has the architectural

characteristics of the ventral and lateral intraparietal areas (VIP/LIP; see section C), and in a caudal region, which is likely to correspond to the medial intraparietal area (MIP; see sections D–E). Finally, weaker projections were observed to originate from the ventral subdivision of the posterior parietal cortex (fields OPt and TPt, in section B), from the ventral inferior temporal (ITv) and parahippocampal (TF) regions, and from the frontal cortex within and around the frontal eye field [area 8Av of Burman et al. (2006)]. While this areal pattern was consistently observed, the exact location of the labeled patches and, in some cases, the density of the projections, varied depending on the visuotopic location of the injection sites. Variations related to visual topography were best appreciated with reference to the well characterized V1 map, but were also reflected in other visual areas, albeit in a less precise manner (probably reflecting their larger receptive fields, and second-order representation maps). There was clear evidence of visual topographic order in the projections from V2, MT, and VLP to DM, and more subtle topo-

graphic trends in the projections from VLA, MTc, and from the area(s) forming the cortical belt immediately rostral to DM.

As shown in Figures 6 and 7, injections placed in the lateral portion of DM, and away from the V2 border, resulted in label that was concentrated in the ventral part of V1, corresponding to the upper (+) quadrant representation. In these same cases (CJ42-DY and CJ52-FR), the densest projections were also clearly concentrated in the ventral portions of V2, VLP, and MT, which, as summarized in Figure 2, represent the upper quadrant. In comparison, the projections from VLA and from the MTc were less clearly organized according to upper versus lower quadrants, instead showing only a slight bias toward concentration of label in the ventral portions of these areas. The projection from the MTc, in particular, often seemed to originate from multiple patches covering much of the extent of this area, albeit with “hot spots” that appeared to reflect its visual topography (Rosa and Elston, 1998). In both Figures 6 and 7, labeled cells in the cortex rostral to DM were concentrated laterally, in the region originally defined as forming the upper quadrant representations of areas DA and DI (Rosa and Schmid, 1995).

Injections that were placed at slightly more medial locations within DM (Figs. 5, 8, 9A) resulted in a more balanced distribution of label across the upper and lower (–) quadrant representations of V1, V2, MT, and VLP. Among these, a caudal injection (Fig. 8) resulted in label concentrated near the representation of the horizontal meridian in V1, while showing a quantitative bias toward the upper quadrant representation of this area. In comparison, sequentially more rostral injections, at approximately the same mediolateral level, revealed a progressive distinction of the upper and lower quadrant labeled zones in V1, from being separated by a slightly less densely labeled gap in CJ35-FR (Fig. 5) to a near-complete segregation in CJ44-FB (Fig. 9A). These observations are significant in that they support the existence of a “map discontinuity” (Van Essen et al., 1981) type of second-order representation, whereby nonadjacent portions of the upper and lower quadrant project to adjacent locations along the rostral border of DM (Rosa and Schmid, 1995). Consistent with the results of electrophysiological mapping (Fig. 2, inset), the labeled cells in the upper quadrant representation of V1 of CJ35-FR and CJ44-FB corresponded to a more eccentric visual field location, in comparison to those in the lower quadrant representation. In each of these cases, the quantitative biases toward upper (Figs. 5, 8) or lower (Fig. 9A) quadrant representations observed in V1 were replicated in areas V2, MT, and VLP, as well as (to a lesser extent) in VLA and the MTc (note that in case CJ44-FB the impression of two segregated patches within MT is likely to reflect, at least in part, masking of labeled cells by the DY injection shown in Fig. 9B). In the cortical belt rostral to DM, the regions of densest label reached further dorsally in comparison with the cases illustrated in Figures 6 and 7, invading

Figure 5. Distribution of label after a tracer injection in DM (case CJ35) (see also Figs. 1, 4). The main panel shows an unfolded representation of the right hemisphere, prepared in the style shown in Figure 1, with the injection site shown in concentric black (core) and white (halo) zones. Thick solid lines indicate the main cortical folds such as the lateral, intraparietal, calcarine, and superior temporal sulci, and the limits between the medial, dorsal, ventral, and orbital surfaces. Histological transition zones between areas are indicated in semitransparent gray, and estimated borders (i.e., borders that could not be visualized directly in this case, but were drawn based on previous results in other animals) are shown in dotted gray lines. To help visualize the borders of DM in regions of dense label, the myeloarchitectural transition zone of this area is highlighted with thin dark lines. The number of labeled cells within $400 \times 400 \mu\text{m}$ regions is indicated as a percentage of the maximum value using the color scale shown on the bottom right (maximum count in this case: 15 cells per unit area). The total number of cells counted in this case was 4158. Scale bar, 2 mm. The red dashed line overlying the V1 map indicates an estimate of the boundary between the upper (V1+) and lower (V1–) quadrant representations. The inset on the top left indicates the visuotopic extent of the injection site, as projected to a diagram of the contralateral hemifield (numbers indicate eccentricities; black lines indicate the limits of the left hemifield; VM, vertical meridian; HM, horizontal meridian). In this diagram the red region encompasses the region estimated by the location of labeled cells in V1 (red), and the white rectangles correspond to the receptive fields recorded closest to the injection site.

the putative lower quadrant representation of DA, which is located near the dorsal midline (Rosa and Schmid, 1995).

Medial injections in DM resulted in a strong concentration of label on the dorsal portions (lower quadrant representations) of V1 and other topographically organized areas, with eccentricity increasing from sites located on the exposed dorsal surface (Fig. 10) to those involving the midline (Figs. 11, 12). In parallel, the densest aggregations of labeled cells in the cortical belt rostral to DM migrated gradually from lateral to medial (for example, these injections resulted in little label in the DI region, and in the lateral part of DA) (Figs. 10–12). Finally, the injection that reached deepest parallel to the midline (Fig. 11) also resulted in label that invaded the representation of the peripheral upper quadrant near the horizontal meridian, as expected from the fact that this part of the visual field is represented as a separate “island” in medial DM (Fig. 2, inset). The distribution of labeled cells observed in these cases supports the visuotopic features of DM in the marmoset defined by Rosa and Schmid (1995). In combination with quantitative analysis reported below, these data support the view that the territory we currently recognize as DM can be justifiably regarded as a single area, which is defined by a stereotyped pattern of cortical afferents.

Projections from V1 and V2

Area V1 was by far the main projection to DM, containing 41% of the labeled neurons (data pooled from 6 cases; range: 30.8–52.9%

Figure 6. Distribution of label after an injection of DY in the representation of the upper visual quadrant in DM. The borders of DM near the injection site are indicated by the thick dark dashed line. Total count = 3227 cells, maximum = 25 cells per unit area. Other conventions are as in Figure 5.

Figure 7. Distribution of label after an injection of FR in the representation of the upper visual quadrant in DM. Total count = 2351 cells, maximum = 20 cells per unit area. Conventions are as in Figure 5.

across different cases) (Fig. 13), while V2 formed the second-largest (13.5%) projection (range 11.1–17.1%). Based on the laminar distribution of labeled cells, these areas formed the only projections to DM that could be unambiguously classified as be-

ing feedforward in nature (Table 2). The V1 projection was almost exclusively formed by supragranular neurons (%SLN = 99.7). In agreement with previous studies (vogt Weisenhorn et al., 1995; Rosa et al., 2005), the majority of neurons projecting to DM were located deep in layer 3 [i.e., in what is traditionally referred to as Brodmann's "layer IVb" (Casagrande and Kaas, 1994) (supplemental Fig. 1, available at www.jneurosci.org as supplemental material)]. However, unlike in the projections from V1 to area MT, a smaller proportion of projecting cells was also found at intermediate (but not superficial) levels of layer 3. As shown in Figure 4 (e.g., section C), labeled cells typically formed a monolayer deep in the supragranular layers in regions of V1 that formed relatively low densities of connections, while more superficial cells became numerous closer to the centers of the labeled patches. In comparison, the projection from V2 to DM included a larger proportion of infragranular cells (average %SLN = 87.2) (Fig. 14), and included cells at all levels of layer 3.

Projections from the superior temporal cortex: area MT and its "satellites"

Many of the lateral and feedback projections to DM originated from areas commonly thought to be nodes in the dorsal, or occipitoparietal "stream," including the superior temporal areas, which are thought to be part of the "dorsolateral circuit." As in other species of monkey (Desimone and Ungerleider, 1986; Rosa et al., 1993), the superior temporal cortex of the marmoset contains a complex of motion-sensitive areas (Rosa and Elston, 1998). The present study confirmed area MT as one of the most important sources of cortical projections to DM [Spatz and Tigges (1972), their focus #7], containing 7.2% of all labeled extrinsic neurons (range: 5.0–12.0%) (Fig. 13). The MT projection to DM consistently had the characteristics of a lateral connection according to the criteria of Grant and Hilgetag (2005). However, it was distinct from other lateral connections of DM (see below) in showing a slightly more marked predominance of supragranular labeled cells (%SLN = 66.1) (Table 2), in most animals (range = 54.9–74.0%) (Fig. 14).

In addition, significant projections were observed from two areas that are functionally and anatomically associated with MT, the MTc [overlaps in part with the Old World monkey's V4t (Kaas and Morel, 1993; Rosa and Elston, 1998)], and the dorsal portion of the MST (Maunsell and Van Essen, 1983; Krubitzer and Kaas, 1990). Projections from the MTc were relatively

uniform across cases, encompassing 3.7% of the cortical afferents of DM (Fig. 13), whereas projections from MST were weaker, and somewhat more variable (range: 0.1–2.7% of all projections to DM). Projections from the MTc and MST were characterized by low %SLN values (32.5 and 25.0, respectively), which firmly placed these in the feedback category (Fig. 14). Finally, we observed isolated labeled cells in the dorsal subdivision of the fundus of the superior temporal area (FSTd) (Kaas and Morel, 1993) to DM. This minor projection (0.1–0.9% of label) consisted predominantly of infragranular neurons (%SLN = 13.3).

Projections from other dorsal and medial extrastriate areas

The cortical belt located immediately rostral to DM, at the dorsal occipitoparietal transition, provides a relatively direct anatomical link between the extrastriate and somatomotor cortices (Burman et al., 2006). For example, even a slight involvement of this region in case CJ25-FE (Fig. 12) was sufficient to reveal additional label in the caudal frontal cortex (which extended to the facial representation of the motor cortex and somatosensory area 3a), and in the rostral parietal cortex. The lateral portion of this belt [putative dorsointermediate (DI) and dorsoanterior (DA) fields, in Fig. 2], which contains neurons with robust visual responses and well defined receptive fields, is likely to encompass homologs of the Old World monkey's caudal intraparietal areas, probably including portions of V3A (Nakamura et al., 2001). In contrast, visual responses tend to be more capricious near the dorsal midline, where receptive fields are larger and extend well into the visual periphery. It has been hypothesized that this region ["medial subdivision of the posterior parietal cortex" (PPm) in Fig. 2] corresponds to the macaque's area V6A (Burman et al., 2006). However, it remains unclear whether DI, DA, and PPm refer to functionally distinct areas, or to different sectors of a functional gradient [for discussion of this problem, see Rosa and Schmid (1995)]. As described above, we observed that the location of labeled patches basically reflected the visual topography described by Rosa and Schmid (1995), with the upper quadrant represented laterally [sometimes as 2 distinct patches of label (Fig. 6)] and the lower quadrant medially. However, given the absence of a robust architectural criterion to delimit these subdivisions, and the ambiguity of the functional data obtained to date, we considered labeled cells throughout the cortical belt rostral to DM together, for the purposes of quantitative analyses.

Our results revealed that this belt is one of the most important sources of afferents to DM, containing 12% of all labeled cells (Fig. 13). Averaging throughout the extent of this region, the projections to DM showed a slight infragranular bias, which was consistent with a feedback connection (%SLN = 35.7, pooled across 6 cases) (Table 2). However, the quantitative results obtained after some injections approached the threshold criterion that indicated a lateral connection (%SLN range: 32.3–39.5) (Fig. 14). As shown in Figure 4 (sections C–E), regions containing a

Figure 8. Distribution of label after a FB injection in caudal DM, which involved the upper and lower quadrant representations. Total count = 8085 cells, maximum = 41 cells per unit area. Conventions are as in Figure 5.

large proportion of supragranular cells were interleaved with others where most cells were located in the infragranular layers. This pattern was observed regardless of whether the label was concentrated in the DA, DI, or PPm subregions.

The cortex on the medial surface, between V2 and the splenium of the corpus callosum, appears to be particularly involved in the analysis of the far periphery of the visual field. It has been suggested that this forms a subcircuit of the dorsal stream involved in the control of postural and defensive reactions (Palmer and Rosa, 2006b). We found that injections in the peripheral representations of DM, involving either the upper or lower quadrant representations (Figs. 4, 5, 9A, 11), resulted in labeled cells in the field adjacent to V2 (here referred to as 19m) (Figs. 2, 3), which is visuotopically organized (Allman and Kaas, 1976; Rosa and Schmid, 1995) but as yet still poorly characterized. Projections from 19m were of variable strength, representing only 0.1–0.2% of labeled cells after the most central injections in our sample (Figs. 6, 8, 11), but 9.9% after the peripheral injection shown in Figure 11. However, they consistently had the characteristics of a lateral connection (%SLN = 50.9) (Fig. 14). In addition, two of the injections labeled isolated neurons in area prostriata, located in the calcarine sulcus rostral to V1 and V2 (Figs. 5, 6).

Projections from the posterior parietal cortex

Both the dorsal (PPd) and ventral (PPv) subdivisions of the posterior parietal cortex send feedback projections to DM, although the %SLN were consistently higher in the former (%SLN = 25.8) than in the latter (%SLN = 4.9) (Table 2). For example, in Figure 4 it is apparent that supragranular cells are relatively common in

Figure 9. *A*, Distribution of label after a FB injection in rostral DM, which was centered in the central (5°) representation of the lower quadrant, but also involved the representation of the peripheral upper quadrant. Total count = 4549 cells, maximum = 20 cells per unit area. *B*, In this same animal, a DY injection was placed in area MT. Total count = 16,268 cells, maximum = 64 cells per unit area. In each panel, the regions where labeled cells may have been obscured by the other injection site are indicated as gray ovals. Other conventions are as in Figure 5.

dorsal parietal subfields such as LIP/VIP (section C) and MIP (section E), whereas they are rare in ventral parietal subfields Opt and TPt (section B).

The majority of the posterior parietal projections to DM originate in subfields of PPd, which together contained 4.7% (range = 2.5–8.8%) of neurons labeled by DM injections. While the densest aggregations of labeled cells occurred in the lateral portion of PPd (LIP/VIP), there was also consistent involvement of a more medial field (which we deem a likely homolog of MIP,

based primarily on relative location). While separate patches attributable to these subfields were observed in most cases (Figs. 5–7, 9A, 10), this was not always the case (Figs. 11, 12). Finally, in some cases (Figs. 6, 9A, 10, 11) isolated cells were observed in the midline parietal cortex, within the architectural limits of the caudal cingulate cortex (area 23) and the putative medial dorsal parietal area (MDP). However, these cells, which were predominantly located in infragranular layers (Table 2), formed <0.1% of the cortical projection to DM.

The projections from PPv to DM were sparser overall (1.0% of the labeled neurons; range = 0.4–2.1%). They originated primarily from a visuotopically organized region located immediately dorsal to the MTc (Rosa and Tweedale, 2000). Based on its histological characteristics, this is likely to correspond to the macaque's field OPT (Pandya and Seltzer, 1982; Gregoriou et al., 2006) or the dorsal prelunate area (May and Andersen, 1986; Ungerleider and Desimone, 1986). Projections from PG, PF, and TPt consisted primarily of isolated cells (Fig. 4, section B), and were not observed in some cases (Figs. 8, 9A).

In the context of the “two dorsal streams” model, we were interested in establishing whether different parietal regions send projections to DM and MT. For this reason, in one animal we attempted to place injections in matching visuotopic locations in these areas (Fig. 9). Analysis of the location of labeled cells in V1 and V2 demonstrated that partial overlap was achieved, although the DM injection site crossed further from upper to lower quadrant representation, and the MT injection labeled a larger number of cells overall. Nonetheless, the patches of posterior parietal cells labeled by the DM injection were exactly overlaid upon those projecting to MT, occupying an elongated region which started caudally near the midline (MIP), but extended rostrally to the LIP/VIP region.

Projections from ventral stream areas

As shown in Figure 2, the lateral extrastriate cortex of the marmoset contains two topographically organized areas, VLP and VLA (Rosa and Tweedale, 2000). While VLA corresponds well to the macaque's V4, there is only a partial overlap between VLP and the most commonly depicted definitions of area V3 (Rosa et al., 2000b; Rosa and Manger, 2005). These areas form strong projections to the inferior temporal cortex (Steele et al., 1991; Weller and Steele, 1992), indicating that VLP and VLA are early stations of the ventral stream. In addition, the inferior temporal cortex rostral to these areas has been subdivided into a topographically organized caudal field [ITc; likely to correspond to TEO of

Boussaoud et al. (1991)] and two nontopographically organized fields (ITd and ITv) (Palmer and Rosa, 2006a).

We found that VLP and VLA both send substantial projections to DM, although these vary in strength (Fig. 13). The most central injections in our sample (Figs. 6, 8) resulted in relatively large numbers of labeled cells in both VLP (e.g., 7.6 and 12.5% of labeled cells) and VLA (7.9 and 8.8% in the same cases), characterizing these as major connections. In contrast, injections in the peripheral representations revealed smaller projections from these areas (Figs. 11, 12). Finally, projections from the ITc to DM were quite limited throughout our data set (0–1.0% of labeled neurons, in different cases). These projections only originated in a restricted region located near the caudal end of ITv, just lateral to the architecturally defined parahippocampal field TF (see below). Projections from VLP, VLA, and ITv to DM showed progressively lower average %SLN values (Fig. 14). While the projections from VLP were consistently compatible with their characterization as a lateral connection of DM (%SLN = 49.5; range 43.0–65.4), the situation was less clear with respect to VLA, given that the range of %SLN values observed in different cases (28.6–39.2%) straddled the range from feedback to lateral connections. The few labeled cells observed in ITv were predominantly located in infragranular layers, firmly characterizing this as a feedback connection (average %SLN = 7.5) (Table 2).

Projections from association cortices

Projections from the dorsolateral frontal cortex were observed in every case [see Burman et al. (2006) for additional examples]. The majority of labeled cells (Fig. 4, section B) were located in the marmoset's putative frontal eye field [cytoarchitectural area 8Av of Burman et al. (2006)] and in adjacent granular frontal areas (cytoarchitectural fields 12 and 46). These long-range connections encompassed 0.7% of the neurons labeled by DM injections [between 0.3% and 1.7%, in different cases (Fig. 13)]. Moreover, in most cases a sparse projection (0.1% of all labeled cells) originated in the ventral part of the agranular premotor cortex [fields 6Dc and 6Dr of Burman et al. (2008)]. The projections from both prefrontal and premotor areas to DM involved supragranular and infragranular cells in approximately balanced numbers (%SLN = 62.9 and 64.0, respectively) (Table 2).

Minor projections to DM originated from the infragranular layers of the parahippocampal cortex (0.3% of all labeled cells; %SLN = 0). Most neurons involved in this connection were located in architectural field TF.

Figure 10. Distribution of label after a small injection of FE in the representation of the lower visual quadrant in DM. Total count = 3054 cells, maximum = 22 cells per unit area. Conventions are as in Figure 5.

Figure 11. Distribution of label after an injection of FE along the portion of DM located on the midline cortex, which labeled primarily the representation of the lower visual quadrant in DM, but crossed slightly into the representation of the peripheral upper quadrant. Total count = 3574 cells, maximum = 15 cells per unit area. Conventions are as in Figure 5.

Hierarchical level of DM

Models of the visual cortex as a hierarchical system were initially based on qualitative observations (Rockland and Pandya, 1979; Tiggles et al., 1981; Maunsell and Van Essen, 1983). More re-

Figure 12. Distribution of label after an injection of FE in the most rostral portion of DM, which involved both the dorsal surface and midline cortices. This injection, which corresponded to the representation of the peripheral lower visual quadrant in DM, crossed slightly into the cortical area immediately rostral to DM (PPm), leading to additional labeled regions in the frontal and parietal regions. Note also the increased label in the retrosplenial cortex (area 23v), which is typically only found after injections in the far peripheral representations of extrastriate cortex (Palmer and Rosa, 2006b). Total count = 2467 cells, maximum = 13 cells per unit area. Conventions are as in Figure 5.

Figure 13. Percentages of labeled neurons located in different cortical subdivisions after injections in DM. Data from six animals are illustrated, with the bars arranged approximately in central to peripheral sequence. The abbreviation GFC represents all label located in the granular frontal cortex. See also Table 2. FC, Frontal cortex.

cently, it has been proposed that the proportion of labeled cells located in the supragranular layers (%SLN) provides an objective quantification of the relative hierarchical rank of interconnected areas (Barone et al., 2000; Grant and Hilgetag, 2005). The present analysis, which used the latter approach (Fig. 14), clearly places

DM at a hierarchical level higher than that of V1 and V2. In addition, projections from MT, while within the range proposed for lateral connections in cat cortex (Grant and Hilgetag, 2005), were characterized by a sufficiently distinct %SLN value (66.1), which suggested that this area corresponds to a level intermediate between those of V2 and DM. This proposal is supported by a converse laminar bias in the projection from DM to MT, reported previously [%SLN = 41.2 (Palmer and Rosa, 2006a)]. The only other projections that showed similar laminar biases were those from the frontal cortex. While the latter observation may seem somewhat difficult to reconcile with a strictly caudal-to-rostral hierarchical scheme, it is consistent with previous findings on the connections of other extrastriate areas (Vezoli et al., 2004; Burman et al., 2006).

Lateral connections consisting of nearly balanced numbers of supragranular and infragranular neurons were formed by other areas located in the “third tier” cortex, immediately rostral to V2 (19m and VLP). Although all other projections to DM were best described as having feedback characteristics, there were clear gradations in supragranular emphasis, which suggested multiple levels of processing. For example, the projections from VLA and from the occipitoparietal belt anterior to DM (%SLN = 38.7 and 35.7, respectively) appeared distinct from those originating in PPd (%SLN = 25.8), which in turn differed from those originating in PPv, ITv, and in the parahippocampal areas (%SLN < 10.0). The summary hierarchy depicted in Figure 15, based on these quantitative data, is entirely compatible with the one deduced independently from the pattern of projections to MT (Palmer and Rosa, 2006a,b).

Discussion

Despite DM being one of three main cortical targets of projections of V1 (Krubitzer and Kaas, 1993), our knowledge of this field has remained fragmentary, in comparison with that of other extrastriate areas. Taking advantage of recent advances in our understanding of the New World monkey visual cortex, the present study maps the cortical input to DM, allowing greater insight into its role in visual processing. Our data paint the picture of an early-stage processing area, which exchanges low-level visual information likely

to be relevant for many different perceptual and behavioral tasks. For example, V1 and V2 send the strongest cortical inputs to DM. In addition, consideration of injections throughout this field reveals nearly balanced inputs from MT and its superior temporal

satellites, adjacent occipitoparietal medial areas, and ventral stream areas (Table 2). Within each of these networks, the predominant connections originate in areas corresponding to low hierarchical levels. Thus, while DM may perform computations that ultimately prove important for the guidance of skeletomotor activity, these are likely to be of a sufficiently general nature that they can underpin other visual functions. In particular, the physiological emphasis of DM cells on spatial integration may also provide information that contributes to the analysis of one's self-motion around the environment, as well as long-range contour completion.

Our results revealed no differences between the connections of the upper and lower quadrant representations in DM, hinting at a basic anatomical uniformity. In addition, we observed no projections that exclusively targeted the central or the peripheral representations, although there were centropreperipheral gradients in the relative density of connections from different areas. Rather than indicating the existence of subdivisions within DM, these gradients most likely reflect the distinct ways that primates use information contained in different parts of the visual field (Gattass et al., 1997; Ungerleider et al., 2008). The robust input from early ventral stream areas to the representations of paracentral visual field can be linked to a form-processing capacity, which has been proposed for one of the most likely Old World monkey homologs of DM (V6; see below) in the context of performing quick analyses for guidance of grasping and reaching (Galletti et al., 1999). Given the long latency of skeletomotor activity, connections from ventral stream areas could be relevant to updating and refining computations of object shape and size performed by DM, in time for midtrajectory corrections. Reciprocally, the fact that DM cells summate oriented contours over much larger areas than their classical receptive fields (Lui et al., 2006) could add to a global form-integration capacity (Tanskanen et al., 2008), thereby extending the range of computations performed in other visuotopically organized areas. For example, this capacity to integrate long-range continuity at an early level of cortical processing could facilitate analyses of large objects near the observer by ventral stream areas, which, unlike DM, heavily emphasize foveal and parafoveal vision (Gattass et al., 1988). While conceptually similar interactions between the dorsal and ventral streams have been hypothesized previously (Vidyasagar, 1999; Bullier, 2001; Laycock et al., 2007), these have not yet explicitly incorporated a role of DM in performing fast computations to guide further shape analyses. Finally, electrophysiological studies focusing on the representation of the central 10–20° of the visual field in DM have reported relatively low percentages of strongly direction-selective cells (Baker et al., 1981; Lui et al., 2006), in comparison with those including far peripheral receptive fields (>40%) (Rosa and Schmid, 1995). The latter figure is comparable to that re-

Table 2. Summary of quantitative characteristics of the projections to DM (data pooled from 6 cases)

	Supragranular cells (<i>n</i>)	Infragranular cells (<i>n</i>)	Total labeled cells (%)	SLN%
V1	6882	23	41.0	99.7
V2	1985	292	13.5	87.2
VLP	640	615	7.5	51.0
VLA	338	536	5.2	38.7
ITv	5	62	0.4	7.5
MT	805	413	7.2	66.1
MTc	203	421	3.7	32.5
MST	28	84	0.7	25.0
FST	4	26	0.2	13.3
19m	164	158	1.9	50.9
DI/DA/PPm	722	1300	12.0	35.7
PPd	204	587	4.7	25.8
PPv	8	154	1.0	4.9
GFC	73	43	0.7	62.9
6D	16	9	0.1	64.0
TF/TH	0	36	0.2	0.0
23/MDP	3	7	0.1	30.0

Figure 14. Percentage of supragranular layer neurons (%SLN) in the projections from different cortical areas and regions to DM. Data from six injections are illustrated, using the same conventions as in Figure 13. See also Table 2.

Figure 15. Summary of the results of quantitative analyses of the cortical afferents of DM. The boxes representing each area or region containing labeled cells were arranged vertically according to the %SLN observed in the different projections to DM. The thickness of each connecting line is indicative of the numerical strength of the projections (strongest projections corresponding to the thickest lines).

ported for macaque area V6 (Galletti et al., 1991). Moreover, similar to V1 and MT, cells in the peripheral representation of DM tend to be selective for faster speeds, and to favor centrifugal directions of motion (Albright, 1989; Battaglini et al., 1993).

These physiological differences can be linked to robust connections with MST and 19m in the peripheral representation, and support a participation of DM in the network of areas involved in analysis of self-motion (Rosa and Tweedale, 2001).

Given the model that proposes parallel medial and lateral circuits in the dorsal stream, we were interested in comparing the connections of DM with those of MT. These are both densely myelinated, striate-recipient areas, which contain cells with receptive fields of approximately similar sizes. However, previous work has demonstrated different stimulus selectivities with respect to direction of motion, orientation, and center-surround interactions (Lui et al., 2006, 2007). While our results reveal that projections to DM originate in what is essentially a subset of the fields that project to MT, there were differences in emphasis. Comparing injections in matching visual field locations, one finds that DM receives relatively stronger projections from V1, V2, VLA, and VLP, while MT receives more substantial projections from MST, MTc, and FST, as well as parahippocampal and retrosplenial fields (Palmer and Rosa, 2006b). Projections from MST to DM originated only in its dorsalmost region, while those to MT also involved the ventral region (Fig. 9A,B). Overall, these observations reveal the connections of MT as being more heavily weighted toward the dorsal stream, in comparison with those of DM. Projections from parietal and frontal fields to DM and MT originated from overlapping regions. Although subtle differences may emerge as knowledge of the marmoset parietal cortex evolves, these observations argue against a strict association of DM and MT with different dorsal stream circuits. Rather, both these areas may combine visual inputs from other areas to extract different sets of information, which can be used in multiple contexts. For example, MT cells perform better at segregating object from background based on motion cues, and compute more accurate information about direction of motion and speed (Baker et al., 1981; Allman et al., 1985). In contrast, DM cells preserve a greater degree of orientation selectivity and can summate contours over longer distances. Both sets of computations may be used in the guidance of body movements, as well as for the perception of the motion and shape of objects, in different situations. Thus, the inferred physiological association of DM with the medial circuit of the dorsal stream is perhaps best understood as a consequence of the fact that a large proportion of guided body movements depend on information contained in peripheral vision. Conversely, the expanded foveal representation in MT places this area in a better position to control tracking eye movements (Komatsu and Wurtz, 1988; Lisberger and Movshon, 1999).

Integration of results obtained in different species requires knowledge of homologies in cortical organization. The distribution of labeled cells we report in the marmoset is consistent with results of injections in cortex immediately anterior to dorsal V2 in other New World monkeys, supporting the view that DM also exists in these species (Weller et al., 1991; Krubitzer and Kaas, 1993; Beck and Kaas, 1998). Comparison with Old World simians is less straightforward, as debate remains as to whether DM has an exact homolog, or is an ancestral field that has become subdivided in primate evolution. Based on earlier studies, we have proposed that DM corresponds to a densely myelinated region located in the annectent gyrus and parietooccipital sulcus of the macaque (Rosa and Tweedale, 2001). While this region overlaps primarily with area V6 [or parts of the parietooccipital area (PO), according to another nomenclature (Galletti et al., 2005)], DM has a comparatively larger representation of the visual field below 10° eccentricity. This central representation would

probably extend slightly into what are usually recognized as medial portions of dorsal V3 (V3d) and V3A (Beck and Kaas, 1999; Rosa and Manger, 2005).

In fact, the results of the present experiments closely reflect the findings of studies involving injections in area V6 (and/or PO), and in the medial (densely myelinated) part of V3d of macaques (Colby et al., 1988; Felleman et al., 1997; Galletti et al., 2001). Like DM, these areas receive strong projections from V1, which arise primarily in Brodmann's layer IVb (see supplemental Fig. 1, available at www.jneurosci.org as supplemental material), but also involve more superficial layers. Other strong projections originate in V2, MT, V4t (MTc), and the occipitoparietal transition cortex (V3A, V6A). The main parietal projections originate in the LIP/VIP and MIP regions, although there are smaller inputs from DP/Opt, laterally, and other parietal fields. Connections from ventral areas VP and V4 are robust following lateral injections (in V3d; Felleman et al., 1997), but weak following medial injections [in V6 or PO (Colby et al., 1988; Galletti et al., 2001)]; conversely, projections to MST and other midline cortices are strongest after medial injections. Finally, like V6 and V3d, DM receives extremely sparse projections from the parahippocampal cortex and FST. In summary, the cortical networks projecting to marmoset DM and to the cortex rostral to dorsomedial V2 in the macaque are very similar, supporting the existence of a homologous organization across primates. This is extremely significant considering that the marmoset and macaque have been separated for over 40 million years (i.e., over two-thirds of the evolutionary history of primates), and have very different brain morphologies. As animal models, marmosets offer a number of advantages, including nonconvoluted brains and accelerated development (Burman et al., 2007). Thus, studies of the dorsomedial extrastriate cortex in this species are likely to provide a powerful complementary approach to physiological investigations in larger primates, and noninvasive imaging work.

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