THE JOURNAL OF COMPARATIVE NEUROLOGY 409:131–152 (1999)

Origin of Thalamic Inputs to the Primary, Premotor, and Supplementary Motor Cortical Areas and to Area 46 in Macaque Monkeys: A Multiple Retrograde Tracing Study

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ABSTRACT

The origin of thalamic inputs to distinct motor cortical areas was established in five monkeys to determine whether the motor areas receive inputs from a common thalamic nucleus and the extent to which the territories of origin overlap. To not rely on the rough definition of cytoarchitectonic boundaries in the thalamus, monkeys were subjected to multiple injections of tracers (four to seven) in the primary (M1), premotor (PM), and supplementary (SMA) motor cortical areas and in area 46. The cortical areas were distributed into five groups, each receiving inputs from a specific set of thalamic nuclei: 1) M1; 2) SMA-proper and the caudal part of the dorsal PM (PMdc); 3) the rostral and caudal parts of the ventral PM (PMvr and PMvc); 4) the rostral part of the dorsal PM (PMdr); and 5) the superior and inferior parts of area 46 (area 46sup and area 46inf). A major degree of overlap was obtained for the origins of the thalamocortical projections directed to areas 46inf and 46sup and for those terminating in SMA-proper and PMdc. PMvc and PMvr received inputs from adjacent and/or common thalamic regions. In contrast, the degree of overlap between M1 and SMA was smaller. The projection to M1 shared relatively limited zones of origin with the projections directed to PM. Thalamic inputs to the motor cortical areas (M1, SMA, PMd, and PMv), in general, were segregated from those directed to area 46, except in the mediodorsal nucleus, in which there was clear overlap of the territories sending projections to area 46, SMA-proper, and PMdc. J. Comp. Neurol. 409:131–152, 1999.

Indexing terms: thalamocortical; primate; fluorescent tracers; motor thalamus

The part of the frontal cortex involved in the control of voluntary movements has been subdivided in primates into multiple areas (at least 12) on the basis of various anatomical and functional criteria (for review, see Wiesendanger and Wise, 1992). Despite variations in the nomenclature used by various authors, four principal regions commonly are distinguished: the primary motor cortex (M1 or area 4), the supplementary motor area (SMA or mesial part of area 6), the premotor cortex (PM or lateral part of area 6), and the cingulate motor areas (CMA or areas 23 and 24). More detailed subdivisions of the SMA, PM, and CMA have been proposed on the basis of either functional or morphological criteria or both. For instance, the SMA has been divided into a rostral part and a caudal part (Wiesendanger, 1986), also referred to as "pre-SMA" and "SMA-proper" (Matsuzaka et al., 1992; Tanji, 1994; Inase et al., 1996) or "area F6" and "area F3", respectively (Luppino et al., 1991, 1993; Matelli et al., 1991). PM has been divided into two main regions (see, e.g., Humphrey and Tanji, 1990; Kurata, 1991, 1994; Kurata and Hoffman, 1994): the dorsal PM (PMd) and the ventral PM (PMv). PMd has been subdivided into a rostral part and a caudal part, referred to as F7 and F2, respectively. Similarly, PMv

Grant sponsor: Swiss National Science Foundation; Grant numbers: 3130–025138, 31–28572.90, and 31–43422.95; Grant sponsor: Roche Foundation (Basle, Switzerland); Grant sponsor: CIBA-GEIGY Jubiläums-Stiftung (Basle, Switzerland); Grant sponsor: INSERM (Paris, France); Grant sponsor: Biomed European; Grant number: BMH4 950789.

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Received 30 December 1998; Revised 7 January 1999; Accepted 28 January 1999

corresponds to area F5 rostrally and area F4 caudally (Matelli et al., 1991). In CMA, three subareas have been proposed (Dum and Strick, 1991).

Although these multiple motor areas differ in a number of functional properties related to the preparation and control of movements (for reviews, see Halsband et al., 1994; Tanji, 1994; Boussaoud et al., 1996), their specific role has not been fully clarified. One essential step is to establish in detail their connections with each other (corticocortical projections) as well as with subcortical structures. Differences and similarities across motor cortical areas regarding their connectivity might reveal functional specializations. In general, the connections of each motor area have been studied separately by using experiments with a single tracer or, less frequently, two tracers (double labeling).

With respect to the thalamocortical projection, M1 receives substantial inputs from the thalamic nuclei: ventroposterolateral nucleus, oral part (VPLo); ventral lateral nucleus, oral part (VLo); ventral lateral nucleus, caudal part (VLc); and ventral lateral nucleus, medial part (VLm). Their respective contributions vary as a function of the precise location of the injection site in M1 (Kievit and Kuypers, 1977; Jones et al., 1979; Schell and Strick, 1984; Leichnetz, 1986; Matelli et al., 1989; Orioli and Strick, 1989; Nakano et al., 1992, 1993; Shindo et al., 1995). In the hand representation of M1, the crest region and the rostral bank of the central sulcus have different connectivity (Holsapple et al., 1991). VLo projects mainly to the sulcus, whereas VPLo projects predominantly to the hand area on the crest of the precentral gyrus. Injections of wheat germ-agglutinin conjugated to horseradish peroxidase (WGA-HRP) into the PMd labeled neurons in the thalamic nuclei: the ventral anterior nuclei (VA), area X, VLc, VLm, and caudally in the mediodorsal nucleus (MD; Nakano et al., 1993). In the same study, after deposit of WGA-HRP into PMv, retrograde labeling was observed in VA, VLm, area X, ventral posteromedial nucleus (VPM), and MD. For PMv, it was found that inputs to the rostral zone (F5) originate mainly from area X with additional projections coming from the VPLo-VLc complex, whereas the caudal zone (F4) receives inputs mainly from VLo with additional contributions from area X and the VPLo-VLc complex (Matelli et al., 1989). Pre-SMA is the target of thalamocortical projections coming from VA, VLo, area X, MD, VLm, and VLc, whereas the caudal portion (SMA-proper) is connected with the thalamic nuclei VLo, VLc, VPLo, VLm, and MD (Kievit and Kuypers, 1977; Künzle, 1978; Jürgens, 1984; Goldman-Rakic and Porrino, 1985; Wiesendanger and Wiesendanger, 1985; Nakano et al., 1993; Inase et al., 1996; Matelli and Luppino, 1996). For the SMA-proper, quantitatively, the major source of inputs is the VLo (Schell and Strick, 1984; Wiesendanger and Wiesendanger, 1985; Matelli and Luppino, 1996).

More recently, these projections have been studied by using double- or multiple-tracer experiments. After injections of two fluorescent tracers into the proximal and distal forelimb areas of M1, retrogradely labeled neurons formed two separate but closely positioned clusters in the ventral nuclear group (mainly VLo and VPLo) of the thalamus (Tokuno and Tanji, 1993; Inase and Tanji, 1995; Shindo et al., 1995). Studies based on injection of two tracers into the hand representations of M1 and SMA in the same monkey confirmed the wide distribution of retrogradely labeled neurons in the thalamus and showed the presence of both segregated and overlapping territories projecting to M1 and SMA (Rouiller et al., 1994a; Shindo et al., 1995). In a study based on distinct tracers deposited in M1, PM, and SMA in the same animal, motor areas received inputs from several thalamic nuclei. However, each area received inputs from these nuclei in different proportions (Darian-Smith et al., 1990). An important observation of the latter report was that the thalamic territories projecting to M1, PM, and SMA clearly transgressed cytoarchitectonic boundaries, an observation that has been confirmed by other studies (Matelli et al., 1989; Nakano et al., 1993; Rouiller et al., 1994a; Matelli and Luppino, 1996).

By using three tracers in the same monkey, Kurata (1994) studied the origin of the thalamocortical projections to the forelimb regions of M1, PMd, and PMv. Cells projecting to M1 were found in VPLo, VLc, and VLo, whereas those directed to PMd were located in VLo and VLc. For PMv, the origin of the thalamic projection was essentially area X and VPLo. More importantly, results from this multiple tracing study indicated a virtual absence of an overlap of these three thalamic territories, which project to M1, PMd, and PMv (Kurata, 1994). The origin of the thalamocortical inputs to PMd were studied in detail (Matelli and Luppino, 1996), distinguishing the rostral part (F7) from the caudal part (F2). It was found that inputs to F2 come from VLc, VPLo, VLo, and MD,

Abbreviations

Cd	caudate nucleus
CL	central lateral nucleus
CM	central median nucleus
CMA	cingulate motor areas
CS	corticospinal
GL	lateral geniculate nucleus
GM	medial geniculate nucleus
ICMS	intracortical microstimulation
LP	lateral posterior nucleus
M1	primary motor cortical area
MD	mediodorsal nucleus
PC	paracentral nucleus
PM	premotor cortex
PMd	dorsal premotor cortex
PMdc	caudal zone of the dorsal premotor cortex
PMdr	rostral zone of the dorsal premotor cortex
PMv	ventral premotor cortex
PMvc	caudal zone of the ventral premotor cortex
PMvr	rostral zone of the ventral premotor cortex
pre-SMA	rostral part of the SMA
PUL	pulvinar nucleus
RT	reticular nucleus of the thalamus
SMA	supplementary motor cortical area
VA	ventral anterior nucleus
VLc	ventral lateral nucleus, caudal part
VLm	ventral lateral nucleus, medial part
VLo	ventral lateral nucleus, oral part
VLps	ventral lateral nucleus, pars postrema
VPI	ventral posteroinferior nucleus
VPLc	ventroposterolateral nucleus, caudal part
VPLo	ventroposterolateral nucleus, oral part
VPM	ventral posteromedial nucleus
VPMpc	ventral posteromedial nucleus, parvicellular part
WGA-HRP	wheat germ-agglutinin conjugated to horseradish peroxidase
X	area X (Olszewski)

TABLE 1. Summary of the Protocol of Injections[1]

Area	Monkey 1 (M. mulatta)	Monkey 2 (M. mulatta)	Monkey 3 (M. fascicularis)	Monkey 4 (M. mulatta)	Monkey 5 (M. mulatta)
Primary motor cortical area	BDA (12 µl; 4,6)	FR (4 µl; 2,4)	DG (1.2 µl; 2,4)		
Supplementary motor cortical area		BDA (9 µl; 3,6)	BDA (4 µl; 2,4)		
Dorsal premotor cortex					
Caudal zone		WGA (0.9 µl; 2,4)	FR (1 µl; 2,4)	CB (7.5 µl; 2,4)	DY (0.6 µl; 2,4)
Rostral zone	FB (0.8 µl; 4,8)		DY (0.4 µl; 2,4)	DY (0.4 µl; 2,4)	CB (4 µl; 2,4)
Ventral premotor cortex					
Caudal zone	DY (0.8 µl; 4,4)			WGA (0.8 µl; 2,4)[2]	FB (0.7 µl; 2,4)
Medial zone			FB (0.8 µl; 2,4)[3]		
Rostral zone				FB (0.8 µl; 2,4)	
Area 46					
Superior		FB (0.4 µl; 2,4)	WGA (1.2 µl; 3,6)		BDA (5 µl; 5,18)
Inferior	WGA (0.8 µl; 2,4)	DY (0.4 µl; 2,4)	CB (1.5 µl; 3,6)		BDA (5 µl; 5,18)

[1]BDA, biotinylated dextran amine (5%); CB, cholera toxin B subunit (0.2%); DG, dextran green (5%); DY, Diamidino yellow (3%); FB, Fast Blue (2%); FR, dextran red (10%); WGA, wheat germ agglutinin (2%). To have appropriate survival times for each tracer, BDA and the fluorescent tracers (DG, DY, FB, FR) were injected in a first session of multiple injections, usually 2–3 weeks before the animal was killed. CB and WGA were injected in a second session of injections, generally 2–4 days before the animal was killed. Below each tracer, between parentheses, the total volume injected is indicated, followed by two numbers, which correspond to the number of microsyringe penetrations and the number of sites injected, respectively. This means that, along several penetrations, the tracer was delivered at two different depths with respect to the pial surface.
[2]The injection was located in the caudal zone of the ventral premotor cortex (PMv) but encroached the dorsal premotor cortex/PMv border.
[3]The FB injection in monkey 3 was aimed in the medial zone of the rostrocaudal extent of the caudal PMv; therefore, the tracer most likely spread into parts of both the rostral zone and the caudal zone of the PMv.

whereas inputs to F7 originate from VA, area X, VLc, VPLo, and MD (Matelli and Luppino, 1996). The double-labelling method was suitable to demonstrate that the thalamic inputs to the arm and leg representations of both F2 and F3 are largely segregated (Matelli and Luppino, 1996).

The premotor areas, such as PM and SMA, are the link between motor-effector pathways (M1, spinal cord) and association areas of the prefrontal cortex, in particular area 46 (see, e.g., Bates and Goldman-Rakic, 1993; Lu et al., 1994). Functionally, there is evidence that the prefrontal cortex is involved in initiation, facilitation, and inhibition of motor responses (see, e.g., Goldman-Rakic, 1987; Fuster, 1989). To establish more completely this complex network of connections involving the prefrontal cortex and premotor cortical areas, it is of interest to compare in the same monkey the origin of thalamic inputs to PM and SMA with the origin of the thalamocortical projections directed to area 46. Based on the retrograde transport of HRP, it was found previously that area 46 receives inputs essentially from the thalamic nucleus MD (Goldman-Rakic and Porrino, 1985; Barbas et al., 1991).

Experiments based on injections of multiple fluorescent tracers (up to four) across different cortical areas of the prefrontal and frontal cortices showed very few if any single thalamic neurons labeled with more than one dye (Goldman-Rakic and Porrino, 1985; Darian-Smith et al., 1990; Shindo et al., 1995). These data indicate that thalamic neurons in general do not project, by means of axon collaterals, to more than one prefrontal or frontal cortical area.

Establishing more precisely the similarities and differences of the thalamic inputs to the various motor cortical areas is limited by difficulties in comparing different experiments conducted on different animals in different laboratories and using distinct tracing methods. Such a comparison requires definition of cytoarchitectonic boundaries, which are subjected to uncertainties. Furthermore, it is extremely difficult to address the issue of overlap and segregation of the projections of two distinct motor areas under such circumstances. The present study addresses this question in experiments that were conducted on the same animal by using a multiple-tracing approach to compare directly the spatial distribution of the multiple tracers. In this case, it is not necessary for the comparison to rely on the uncertain definition of cytoarchitectonic boundaries. To reach this goal, several tracers (ranging from four to seven) were injected into different zones of motor cortical areas M1, SMA, and PM as well as into area 46 of the prefrontal cortex, with a special emphasis on establishing the origin of their thalamic inputs and the degree of overlap and segregation of the territories of origin.

Previous studies have used multiple tracers (usually up to three) to compare the origin of thalamic inputs to distinct motor cortical areas (see, e.g., Darian-Smith et al., 1990; Kurata, 1994; Matelli and Luppino, 1996). A first contribution of the present study is to combine from four to seven tracers in a single animal. This will allow comparison in the same animal of a larger set of motor areas (M1, PM, SMA) and prefrontal areas (area 46) with results from studies available in the literature. A second contribution of the present work is to emphasize the issue of overlap versus segregation of the thalamocortical projections to distinct cortical areas rather than on the cytoarchitectonic identification of the nuclei of origin.

MATERIALS AND METHODS

The present data are derived from experiments conducted on five monkeys (*Macaca fascicularis* or *Macaca mulatta*) that were subjected to injections of multiple tracers into distinct motor cortical areas as well as the superior and inferior parts of area 46 (46sup and 46inf, respectively; see Table 1, Fig. 1).

In monkey 1, a rectangular recording chamber was implanted above the left hemisphere under deep anesthesia (initiated with ketamine 5 mg/kg, i.m.; continued with propofol 3 mg/kg/hour, i.v.), providing access to M1, SMA, PM, and area 46. An extensive electrophysiological mapping of M1, SMA, and PM was conducted by using intracortical microstimulation (ICMS) performed during daily sessions lasting 2 hours on average over a 3-week period. The microstimulation technique was the same as that described previously and illustrated in detail for M1 and SMA (Rouiller et al., 1994a,b). This procedure established a detailed somatotopic map of M1 and its rostral border with PMd and PMv as well as a rough estimation of the somatotopy in PMd and SMA. These ICMS data guided multiple injections of retrograde tracers into M1, into the

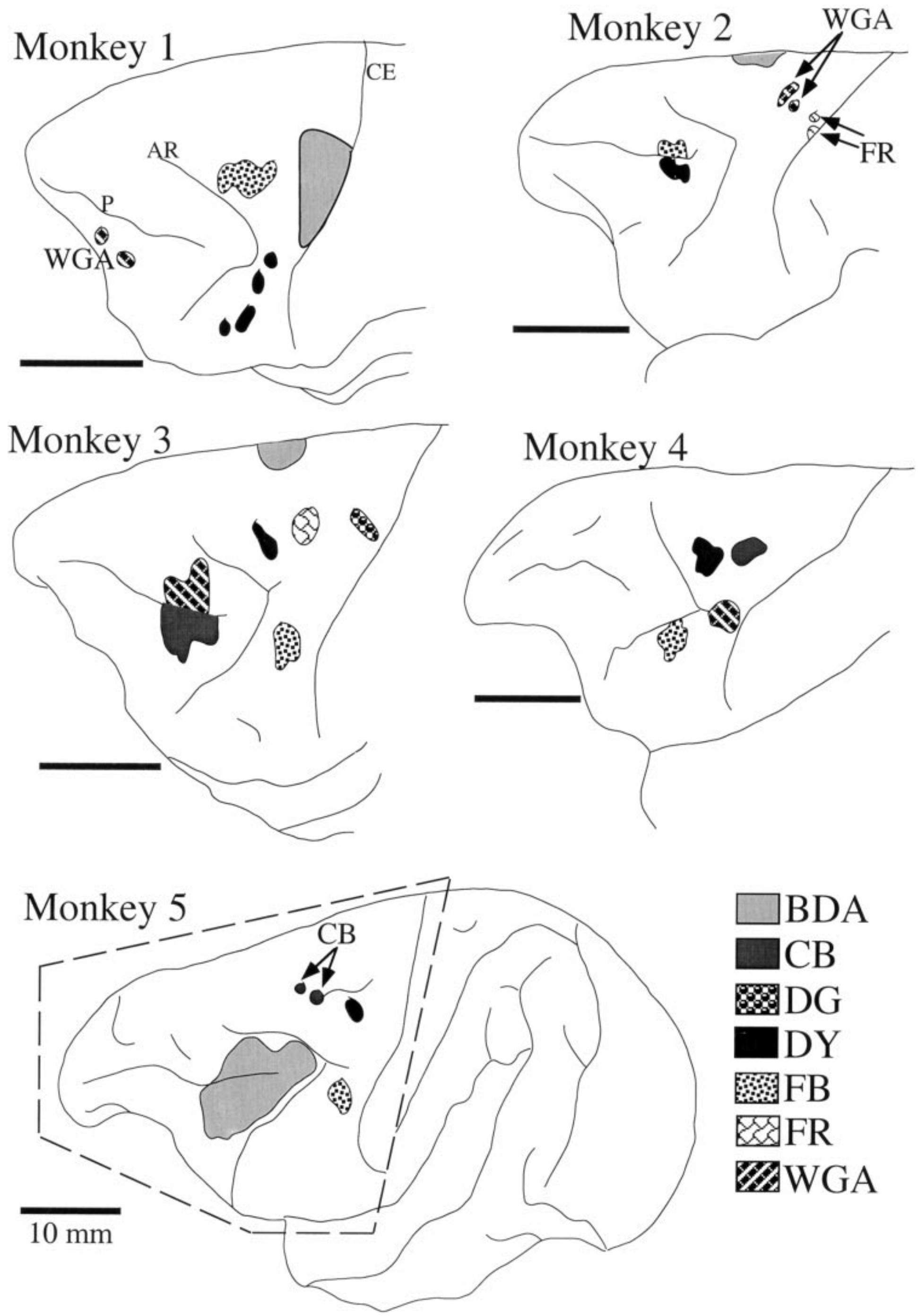

Fig. 1. Lateral view of the left hemisphere of the five experimental monkeys, with location and extent of the injection sites for the multiple tracers. For monkey 5 (bottom), the whole hemisphere is represented. For the other four monkeys, only the frontal lobe is represented (corresponding to the part of the brain outlined with a dashed line in monkey 5). Tracers: BDA, biotinylated dextran amine; CB, cholera toxin B subunit; DG, dextran green; DY, Diamidino-yellow; FB, Fast Blue; FR, dextran red; WGA, wheat germ agglutinin. See Table 1 for indications about volumes and dilutions. AR, arcuate sulcus; CE, central sulcus; P, sulcus principalis. Scale bars = 10 mm.

rostral part of PMd (PMdr), and into the caudal part of PMv (PMvc). Injections into area 46inf were made under visual guidance with respect to the principal sulcus (Table 1, Fig. 1).

In monkey 3, anesthesia was induced with ketamine and was maintained for 1 hour with pentobarbital (30 mg/kg body weight, i.p.), allowing trepanation to expose M1, SMA, PM, and area 46. After fading of the pentobarbital effect, ICMS was conducted under ketamine anesthesia to determine the somatotopy of M1, PMd, and SMA. Thresholds clearly were higher compared with the awake animal (in particular, in SMA; see Rouiller et al., 1994a). The animal was then more deeply anesthetized with pentobarbital (30 mg/kg body weight, i.p.) for tracer injections. The ICMS data guided the injections of tracers into M1, PMd, and SMA, whereas injections into PMv and area 46 were done according to stereotaxic coordinates as well as under visual guidance with respect to the arcuate sulcus and principal sulcus, respectively (Table 1, Fig. 1). The same general protocol of injections was applied to monkey 2, except that no ICMS was performed. Therefore, injections into M1, SMA, and PMd also were done based on stereotaxic coordinates and visual guidance according to the location of the arcuate and central sulci (Table 1, Fig. 1). Similarly, in monkey 4, injections of tracers were aimed at PM (Table 1) based on stereotaxic coordinates and visual guidance with respect to the sulci.

In monkey 5, injections of tracers were made into PM (Table 1) guided by ICMS data and into area 46 based on stereotaxic coordinates and visual guidance, taking into account the principal sulcus. This monkey was used for electrophysiological investigations in PMd while he performed a complex visuomotor task (see, e.g., Boussaoud, 1995; Kermadi and Boussaoud, 1995). These data also provided a basis to guide injections into the rostral (PMdr) and caudal (PMdc) parts of PMd.

In all sessions in which the brain was exposed to perform injections of tracers, animals were treated initially with dexamethasone (Decadron 0.2 mg/kg, i.m.) to minimize brain edema. At the end of each injection session, monkeys were treated daily with injections of the antibiotic *oxytetracyclinum* (Engemycin 10%, 10 mg/kg, i.m. Intervet International B.V. Holland) and the analgesic *metamizolum natricum* (Vetalgin, 100 mg/kg, i.m. Veterinaria AG Zürich Switzerland) during 2–5 days to prevent infection and pain. Following an appropriate survival time for the axonal transport of the tracers (Table 1), the animals were deeply anesthetized with a lethal dose of pentobarbital and perfused through the heart with 500 ml saline followed by 4,000 ml fixative (4% paraformaldehyde). The brain was dissected, postfixed for a few hours, and soaked in a solution of 30% sucrose in phosphate buffer (0.1 M), pH 7.4, for cryoprotection for 5 days. Frozen sections (40–50 µm thick) were cut in the frontal plane by using a freezing microtome, and seven series of sections were collected separately. Two series of sections were mounted immediately on gelled slides, one used for the subsequent analysis of the fluorescent tracers and the other for Nissl counterstaining. Three other series were treated to visualize the nonfluorescent tracers biotinylated dextran amine (BDA), cholera-toxin B subunit (CB) and WGA, as described previously in detail (Rouiller et al., 1993, 1994a,b, 1996, 1998). In those previous reports, the absence of cross-reaction between the nonfluorescent tracers was demonstrated. Two series of sections were kept as reserve. Every other section from each series was reconstructed by plotting contours and the position of the corresponding retrogradely labeled neurons by using a light microscope interfaced with a computer, as previously described (Rouiller et al., 1993, 1994a,b). Then, drawings of adjacent sections containing the data for the different markers were superimposed on top of one another to assess the extent of overlap (or segregation) of the thalamic territories projecting to the cerebral cortex. In addition, they were superimposed to an adjacent series of Nissl-stained sections from which the cytoarchitectonic boundaries were established, as described previously (Rouiller et al., 1994a). This last step was not necessary for the comparison across the different markers: it was indicative of the thalamic nuclei in which labeling was observed. In addition to systematic reconstruction of histological sections based on manual plotting, as described above, some thalamic regions were captured with a color video camera (DXC-C1MDP; Sony, Tokyo, Japan) interfaced to Adobe Photoshop 3.0 software (Adobe Systems, Mountain View, CA) for Macintosh Power PC (Apple Computers, Cupertino, CA; see Fig. 2). Experimental procedures were in accordance with the U.S. National Institutes of Health Guide for Care and Use of Laboratory Animals and the European Community's Guidelines for Animal Protection and Use for Experimentation and were approved by the Swiss veterinarian authorities.

RESULTS

The thalamocortical projections to each motor cortical area, taken individually, are well documented (see above). Therefore, the results are presented below with an emphasis on describing the extent of overlap (or segregation) of the thalamic territories projecting to one or another cortical area of the frontal cortex. We noticed that some tracers provided stable and reproducible results (e.g. Diamidino-Yellow [DY], Fast Blue [FB], and BDA), whereas others gave somewhat more variable results in terms of quality of labeling (CB, WGA, dextran red [FR], and dextran green [DG]). Although all markers were charted with color codes on working reconstructions of single sections of the thalamus, for simplification, the data are presented below by taking markers by pairs. Therefore, we can assess the extent to which the projections to given cortical areas share territories of origin in the thalamus.

The locations of the multiple injection sites, as seen on a surface view of the injected hemisphere, are represented in Figure 1 for the five monkeys included in the present study (Table 1). Photomicrographs of typical injection sites have been shown previously for the nonfluorescent tracers (CB, WGA, and BDA) deposited in M1 or SMA (Rouiller et al., 1994a,b). The typical appearance of retrogradely labeled neurons in the thalamus is shown in Figure 2 for the nonfluorescent tracers used in the present study. It also illustrates the procedure used to delineate a thalamic territory giving rise to a thalamocortical projection as well as examples of isolated labeled neurons. The issue of double-labeled neurons corresponding to a collateral projection from one thalamic neuron to two cortical areas could be addressed here with the pair of tracers FB and DY. Double-labeling was observed very rarely, confirming previous observations (Goldman-Rakic and Porrino, 1985; Darian-Smith et al., 1990; Inase and Tanji, 1995; Shindo et al., 1995; Matelli and Luppino, 1996).

Origin of thalamocortical projections to SMA-proper (F3) and PMdc (F2)

Previous data derived from separate experiments (see above) led to the prediction that PMdc and SMA-proper have some common territories of origin for their thalamocortical inputs, such as the nuclei VLo, VLc, VPLo, and MD (see Kurata, 1994; Matelli and Luppino, 1996). This prediction could be verified directly in monkeys 2 and 3, because each was subjected to injections of BDA in SMA-proper, whereas WGA and FR were injected in PMdc, respectively (Table 1). For both areas, it was found that the main thalamic nucleus of origin was VLo, where there was a significant overlap of the two territories of projection (Figs.

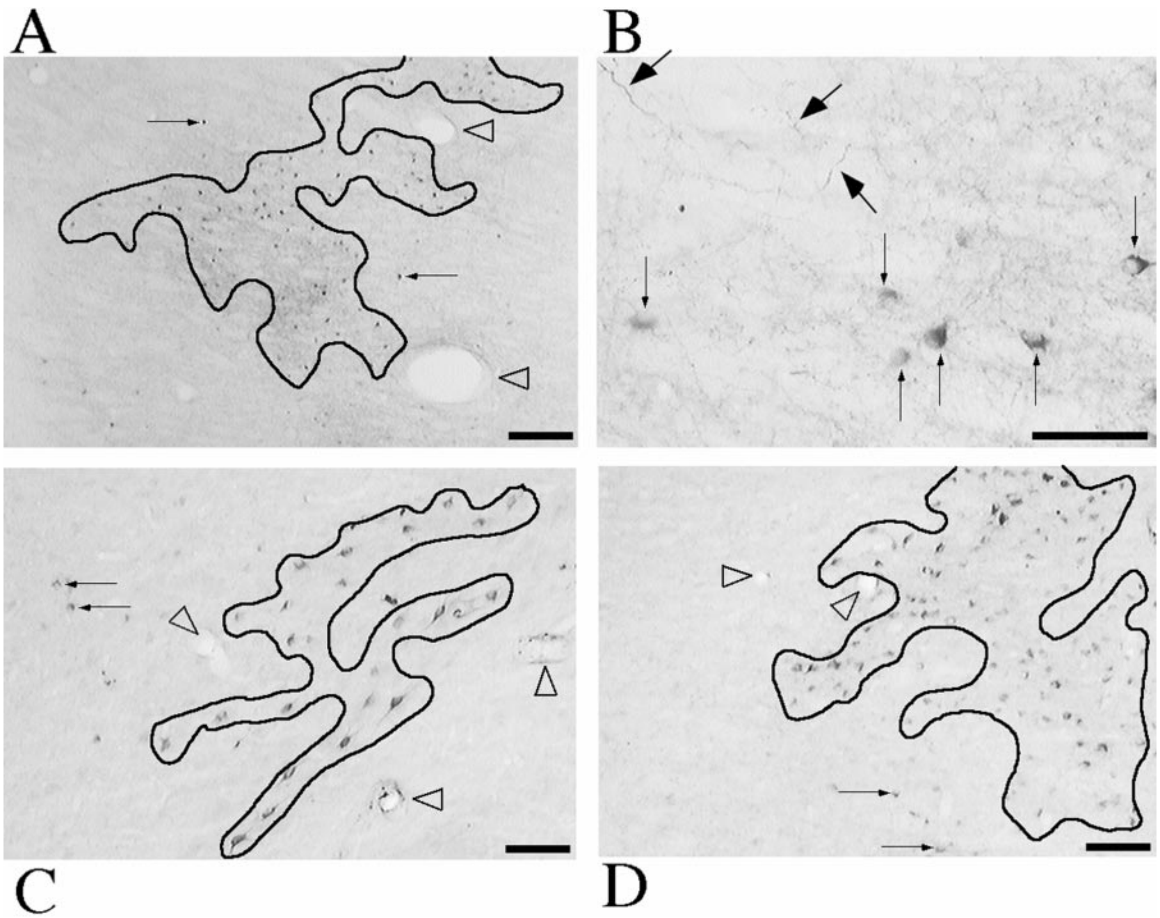

Fig. 2. Photomicrographs illustrating typical retrogradely labeled neurons in the thalamus after injection of three nonfluorescent tracers into different cortical areas. Arrowheads point to blood vessels. **A:** Retrogradely labeled neurons in the ventral lateral nucleus, oral part (VLo), as a result of BDA injection into the supplementary cortical area (SMA) in monkey 3. A cluster of labeled neurons is outlined with a continuous line, illustrating the delineation of territories containing thalamocortical neurons, as represented in Figures 3–13. **B:** A few retrogradely BDA-labeled neurons taken from the cluster of panel A are shown at higher magnification (thin arrows). Thick arrows point to BDA-labelled axon segments. **C:** Cluster of retrogradely labeled neurons in the caudal part of the mediodorsal nucleus (MD) as a result of CB injection into the inferior part of area 46 (46inf) in monkey 3. **D:** Cluster of retrogradely labeled neurons in the caudal part of MD resulting from injection of WGA into the superior part of area 46 (46sup) in monkey 3. In A, C, and D, thin arrows point to isolated neurons outside the cluster of labeled cells. Scale bars = 250 µm in A, 100 µm in B–D.

3, 4). Other nuclei of origin with a variable extent of overlap for the two cortical areas were VA, VPLo, VLm, VLc, and, more caudally, the central lateral nucleus (CL) and MD. For both monkeys, after injections into SMA-proper and PMdc, some thalamic nuclei were relatively free of retrograde labeling, such as area X, the paracentral nucleus (PC), the ventral posteroinferior nucleus (VPI), and VPM. The data obtained for these two monkeys are generally comparable. However, some minor differences in the spatial distribution of both markers were seen (Figs. 3, 4) due to variations in the precise location and size of injections into SMA-proper and PMdc and/or to species (Fig. 1, Table 1). The distribution of the thalamic territories projecting to PMdc observed for monkeys 2 and 3 was consistent with the data derived from CB injections into PMdc of monkey 4 (see Fig. 9).

Origin of thalamocortical projections to area 46sup and area 46inf

In monkey 3, the origins of the thalamocortical projections directed to area 46sup and area 46inf were derived from injections of WGA and CB, respectively (see Fig. 5). At almost all rostrocaudal levels, retrograde labeling for both areas was found mainly in the medial region of the thalamus, essentially in MD, although labeled territories were seen rostrally in VA, PC, and VLm and caudally in CL and the central medial nucleus (CM). Overlap of both markers was observed principally in MD (Fig. 5). Note that no labeling was found in the nuclei VLo, VPLo, area X, the ventroposterolateral nucleus, caudal part (VPLc), VPI, or VPM. The general location, extent, and overlap of the thalamic zones projecting to area 46sup and area 46inf was very similar to that found in monkeys 2 and 5 (in which different tracers were used) and in monkey 1 for area 46inf (in which WGA was injected).

Origin of thalamocortical projections to M1 (F1) and PMv (F4 and F5)

Monkey 3 also was subjected to injections of the fluorescent tracer DG aimed at the hand representation of M1 and the tracer FB in the middle of the rostrocaudal axis of

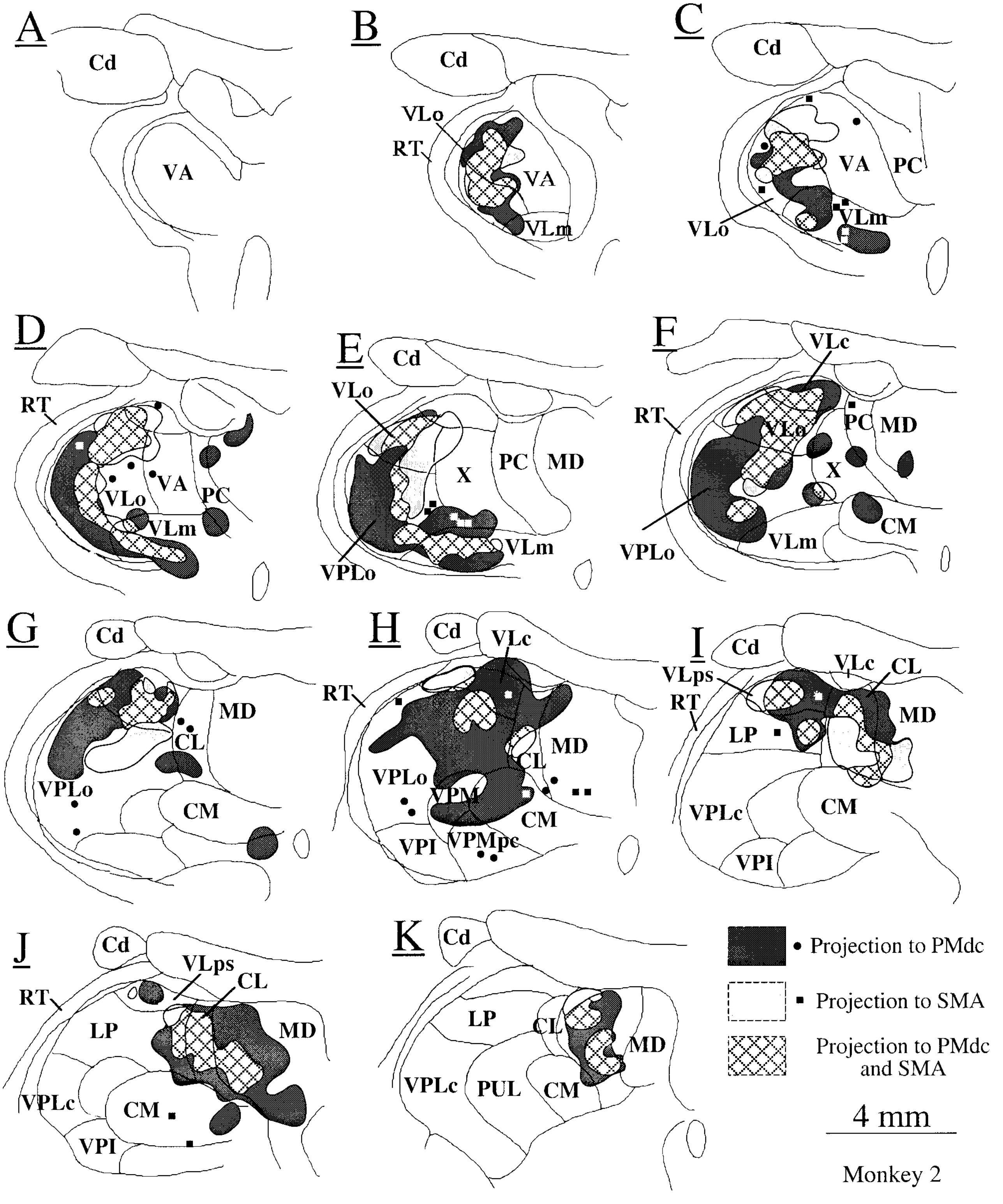

Fig. 3. **A–K:** Spatial distribution in the thalamus of clusters of retrogradely labeled neurons after injections of WGA into the caudal zone of the dorsal premotor cortex (PMdc) and BDA into SMA proper. Data were derived from monkey 2 (see Table 1). The bottom right **inset** identifies the two corresponding types of clusters as well as zones of overlap containing neurons labeled with one or the other tracer. Isolated labeled neurons are represented by circles and squares (projecting to PMdc and SMA, respectively). Reconstructions of frontal sections of the thalamus were arranged from rostral (A) to caudal (K). Consecutive sections are separated by 700 µm. The most rostral section (A) is at stereotaxic rostrocaudal coordinate 14.5 mm. For abbreviations, see list.

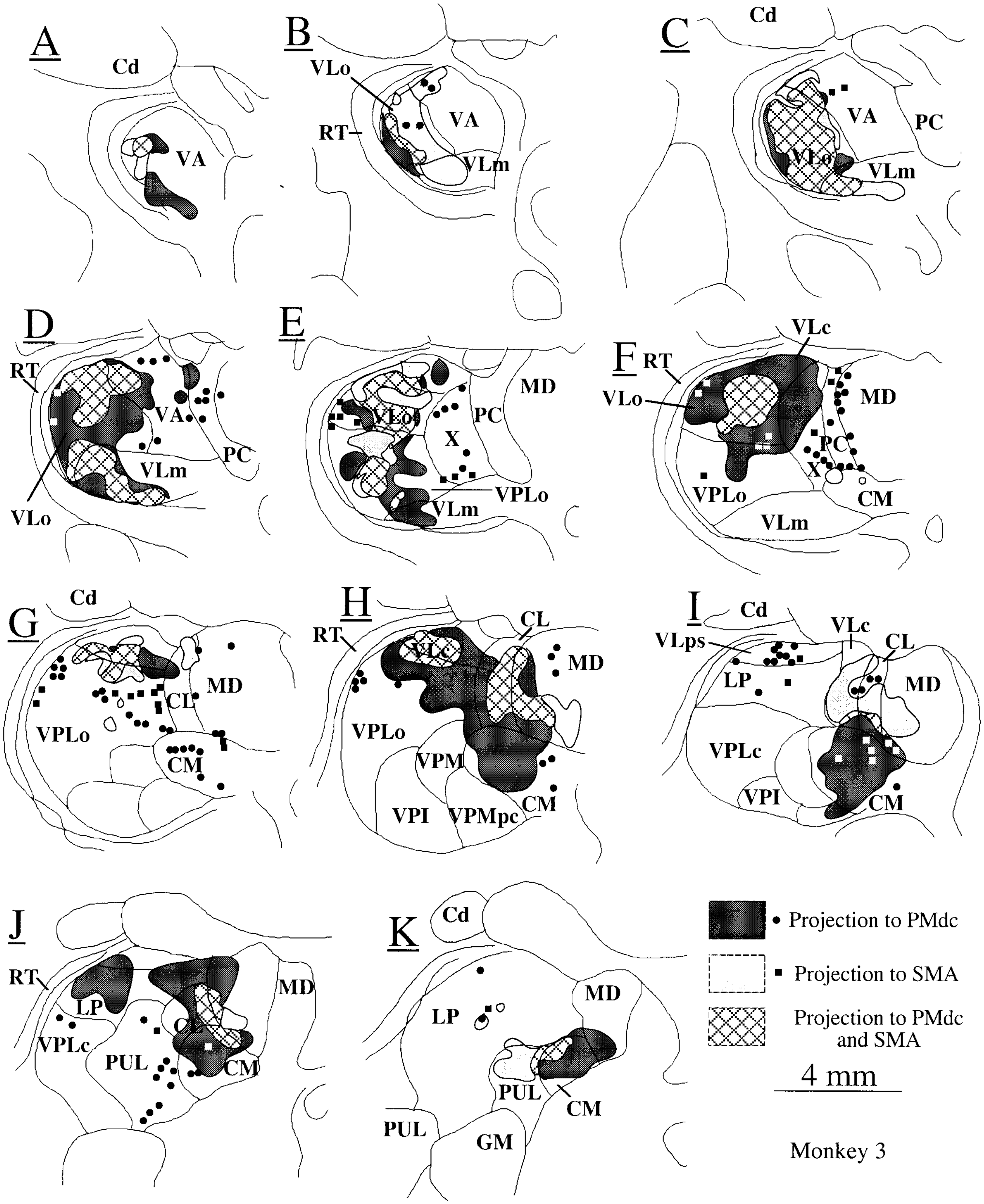

Fig. 4. **A–K:** Spatial distribution in the thalamus of clusters of retrogradely labeled neurons after injections of FR into PMdc and BDA into SMA proper. Data were derived from monkey 3 (see Table 1). For conventions, see Figure 3. For abbreviations, see list.

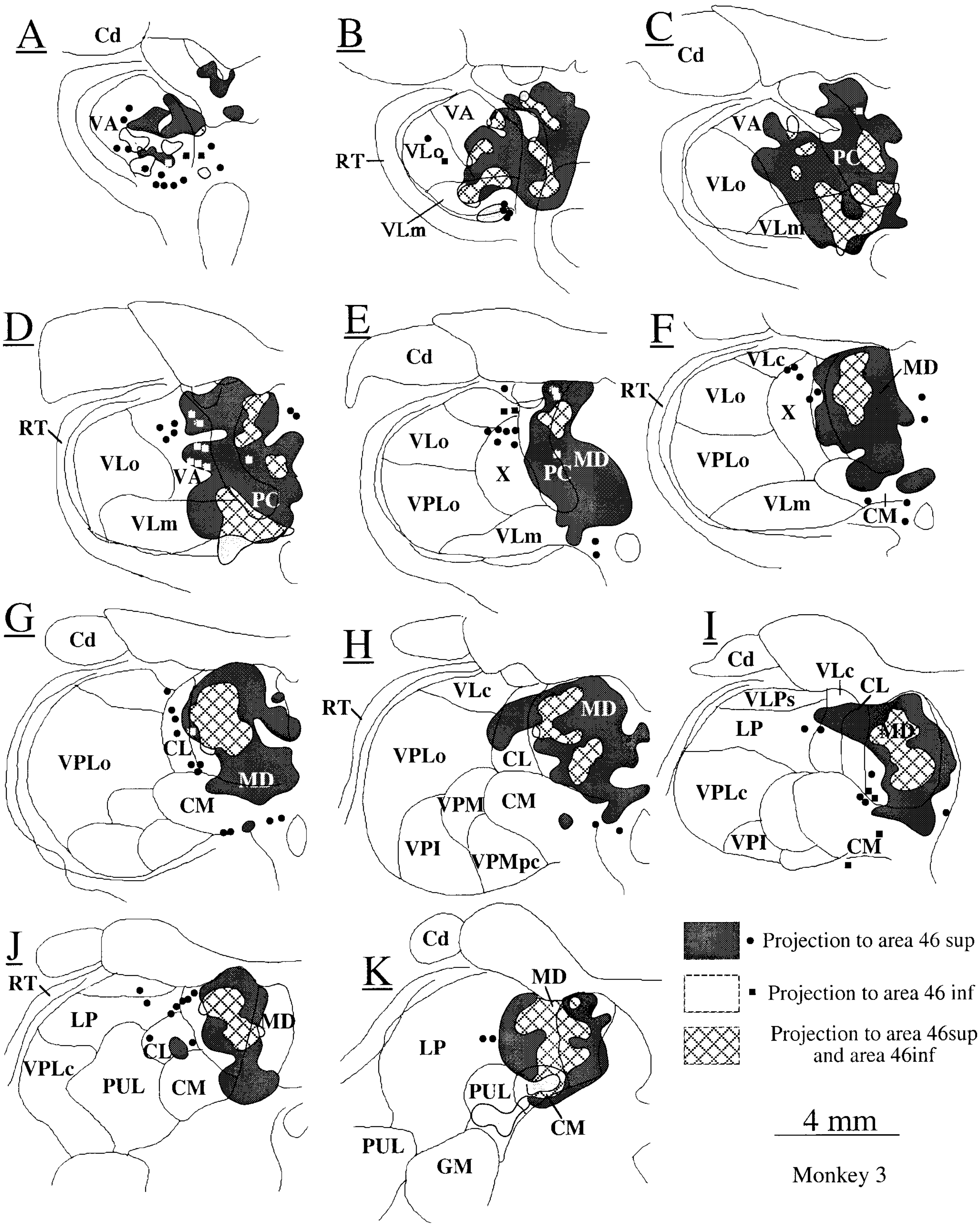

Fig. 5. **A–K:** Spatial distribution in the thalamus of clusters of retrogradely labeled neurons after injections of WGA into area 46sup and CB into area 46inf. Data were derived from monkey 3 (see Table 1). For conventions, see Figure 3. For abbreviations, see list.

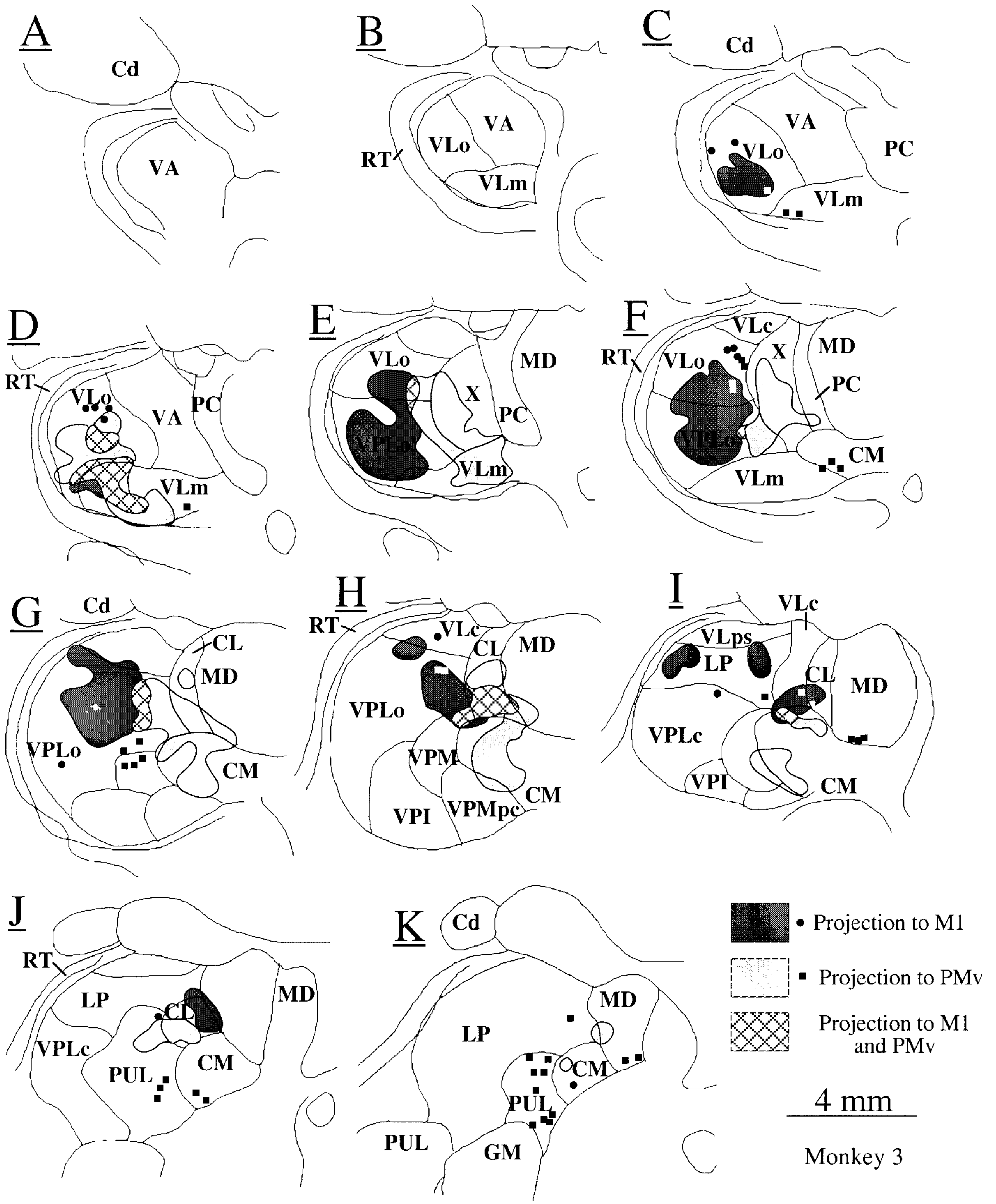

Fig. 6. **A–K:** Spatial distribution in the thalamus of clusters of retrogradely labeled neurons after injections of DG into M1 and FB into PMvm. Data were derived from monkey 3 (see Table 1). For conventions, see Figure 3. For abbreviations, see list.

PMv to tentatively involve PMvr and PMvc (Table 1, Fig. 1). The injection into M1 covered the hand area both in the sulcus and on the crest. DG retrograde labeling was found predominantly in VPLo and VLo (Fig. 6), as expected (see above). Projections directed to PMv originated in this case mainly from area X, although there were some retrogradely FB-labeled neurons in VLo and VPLo, with a limited degree of overlap with the territories projecting to M1 (Fig. 6). In the caudal half of the thalamus, the projection to PMv originated mainly from the nuclei CL and CM, again with little overlap with the M1 projection (Fig. 6). In this particular monkey, there clearly was less overlap between the territories projecting to M1 and PMv compared with that observed for the projections to SMA-proper and PMdc (Figs. 3, 4) and to areas 46sup and 46inf (Fig. 5).

A comparison of the thalamic zones projecting to M1 and PMv also was possible in monkey 1 (Table 1). Consistent with the data from Figure 6, it was found in monkey 1 that the territories projecting to M1 and PMvc are well segregated in the rostral half of the thalamus. In contrast to Figure 6, however, in monkey 1, overlap was more extensive in the caudal half of the thalamus than in monkey 3, particularly in CL. In VLc and MD, there was overlap in monkey 1 but not in monkey 3 (Fig. 6). Again, this variation might be due to differences in the location and extent of the injection sites in M1 and PMv and/or to species (Fig. 1, Table 1).

Origin of thalamocortical projections to the hand representations of M1 (F1) and SMA-proper (F3)

The present data about the origins of the thalamocortical projections to the hand representations of M1 and SMA-proper (Figs. 3, 4, 6) confirm previous observations (see above). When the labeling due to injections of two tracers into the hand representations of M1 and SMA-proper in the same animal (monkey 3) is plotted on single sections, significant zones of overlap are found in VLo and VPLo (Fig. 7). However, the same two nuclei contain large zones projecting to only M1 or SMA-proper. More caudally, there is additional overlap in CL (Fig. 7). However, segregation of the two origins of thalamocortical projections to M1 and SMA-proper is particularly prominent in the rostral pole of thalamus (projecting mainly to SMA-proper; Fig. 7A–C) and in MD (also projecting mainly to SMA-proper; Fig. 7H–J). A very similar pattern of thalamocortical projections to the hand representations of M1 and SMA-proper was observed in monkey 2, also in line with our previous tracing experiments (Rouiller et al., 1994a).

Origin of thalamocortical projections to the four divisions of PM

In two animals (monkeys 4 and 5), emphasis was put on investigating the connectivity of the various subdivisions of PM, namely, PMdc (F2), PMdr (F7), PMvc (F4), and PMvr (F5). These data are derived from the tracers FB, DY, WGA, and CB placed at different locations in these two monkeys (Table 1, Fig. 1).

In PMd, progressive functional changes have been demonstrated along the rostrocaudal axis (Tanné et al., 1995; Johnson et al., 1996). However, it is unclear whether such functional differentiation is correlated with differences in the connectivity and, in particular, with thalamic inputs. In the present series of experiments, the injections of tracers into PMdr in monkeys 1, 3, 4, and 5 (Table 1) labeled thalamic territories of quite variable extents. In monkey 3, for unknown reasons, there was almost no retrograde labeling in the thalamus after injection into PMdr. In sharp contrast, after injection of CB into PMdr (monkey 5), relatively large clusters of retrogradely labeled neurons were observed in the thalamus, principally in VA, area X, VLo, VLc, CL, and MD (Fig. 8). Intermediate between monkeys 3 and 5, the injection of DY into PMdr of monkey 4 produced medium-sized clusters of retrograde labeling in the thalamus that also were distributed across VA, area X, VLo, VLc, CL, and MD (Fig. 9). In monkey 1, after injection of FB into PMdr, the retrogradely labeled neurons were distributed in thalamic zones, as shown in Figure 9, although the clusters of labeled neurons, in general, were smaller. Clearly, the thalamic zones projecting to PMdr were much larger in monkey 5 than in monkey 4 (compare Fig. 8 with Fig. 9). The reverse was true for PMdc: Larger thalamic territories were found to project in monkey 4 than in monkey 5. Overlap between thalamic territories projecting to PMdr and PMdc appeared relatively limited in monkey 5 (Fig. 8), whereas the two territories overlapped almost absolutely in monkey 4 (Fig. 9). This discrepancy might be due to differences in size and precise positions of injections into PMd between the two monkeys (Fig. 1).

Inputs to PMvr and PMvc were found to originate from close thalamic territories of relatively small size (Fig. 10). They were distributed mainly in area X, VLm, CL, and MD. Considering the small extent of these two territories, their degree of overlap can be considered large relative to the total area of the clusters of retrogradely labeled neurons in the thalamus.

Monkey 4 is the only animal in which clear data have been obtained from the injections of four tracers into the four subdivisions of PM. To assess the extent of common versus segregated thalamic inputs to PMd on one hand and PMv on the other, the data from Figures 9 and 10 are represented differently in Figure 11, in which the zones projecting to PMdr and/or PMdc have been put together, and the same, but with another symbol, is true for the zones projecting to PMvr and/or PMvc. For these particular injections and tracers, the origin of the thalamic inputs reaching PMd and PMv, to a large extent, are segregated (Fig. 11). Only very few, small zones of overlap of the territories of origin were observed, and these were restricted primarily to area X, VLm, and CM. This segregation between PMd and PMv was even more prominent when the thalamic zones projecting to PMdr and PMvr or to PMdc and PMvc were plotted together for monkey 4. There were no or very few small zones of overlap.

Origin of thalamocortical projections to M1, PM, and SMA versus to area 46

The origin of the thalamocortical projections to areas 46sup and 46inf is illustrated in Figure 5.

To determine whether the thalamic territories projecting to area 46 overlap with those that send projections to M1, SMA, and PM, the zones of retrograde labeling obtained in monkey 3 are plotted in Figure 12. Because of their relative similarity in terms of origins of thalamocortical inputs, SMA and PMdc are grouped together; a similar grouping, but with another symbol, is shown for areas 46sup and 46inf (Fig. 12). These two territories show some overlap in the most rostral part of the thalamus (Fig.

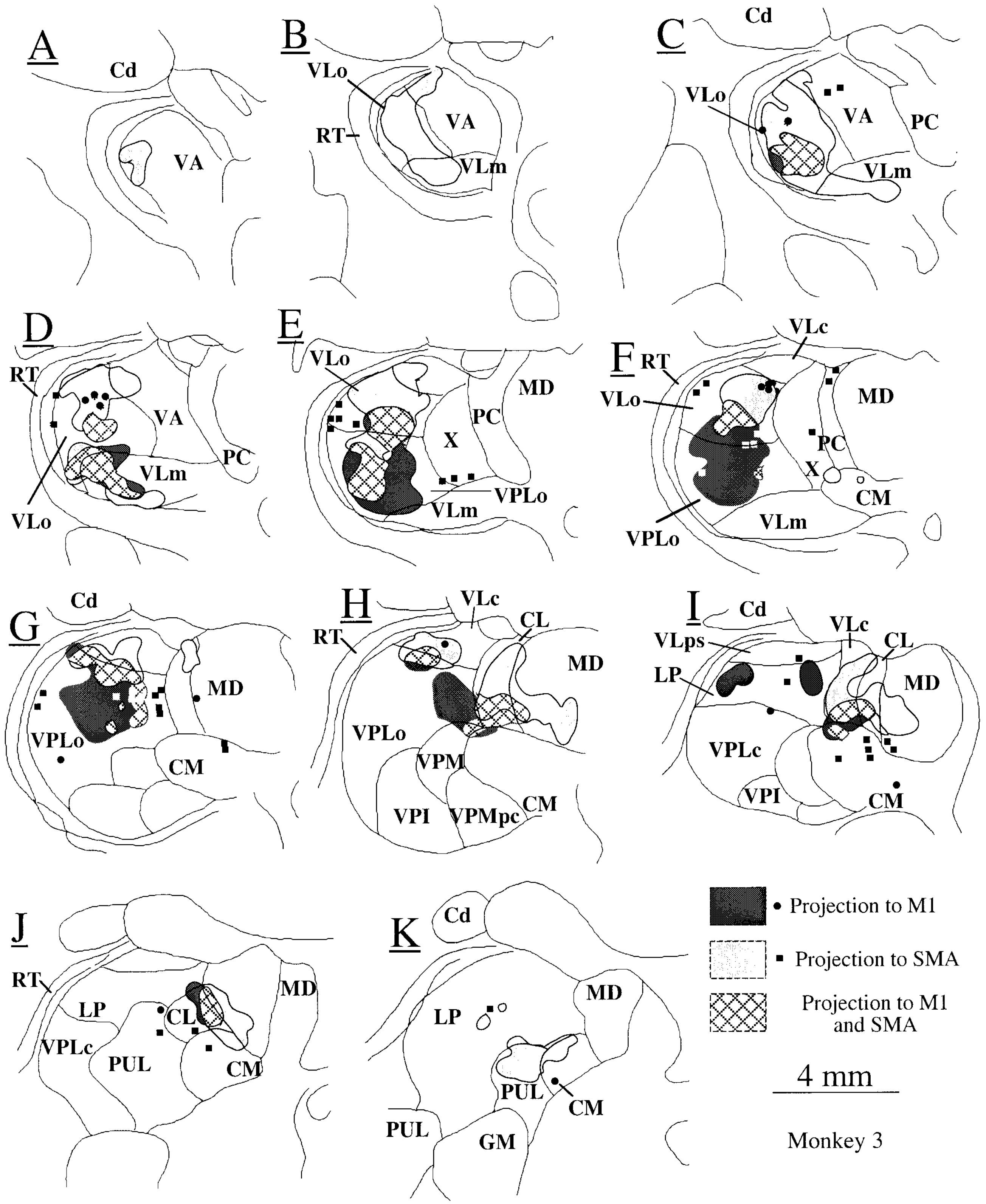

Fig. 7. **A–K:** Spatial distribution in the thalamus of clusters of retrogradely labeled neurons after injections of DG into M1 and BDA into SMA proper. Data were derived from monkey 3 (see Table 1). For conventions, see Figure 3. For abbreviations, see list.

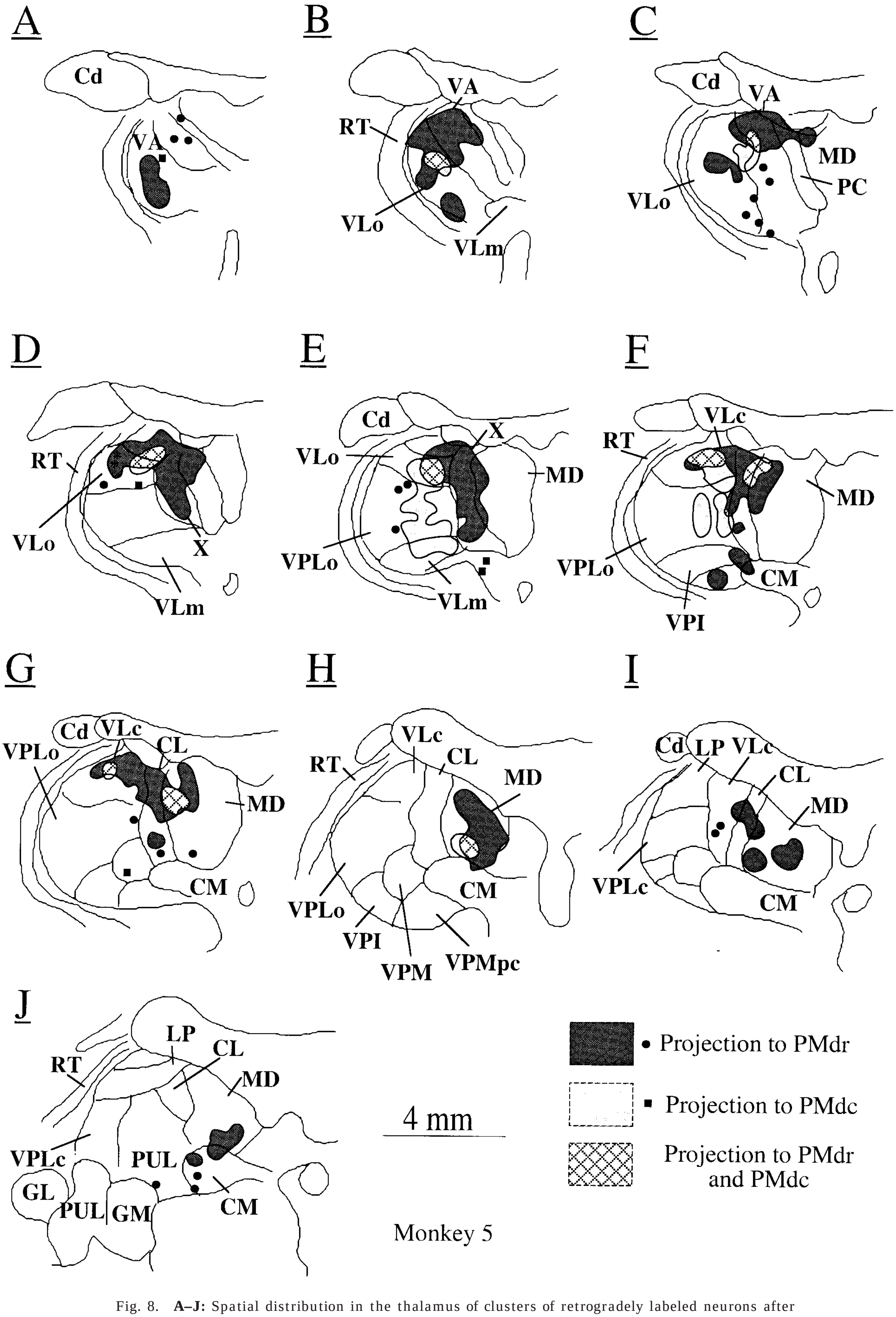

Fig. 8. **A–J:** Spatial distribution in the thalamus of clusters of retrogradely labeled neurons after injections of DY into PMdc and CB into PMdr. Data were derived from monkey 5 (see Table 1). For conventions, see Figure 3. For abbreviations, see list.

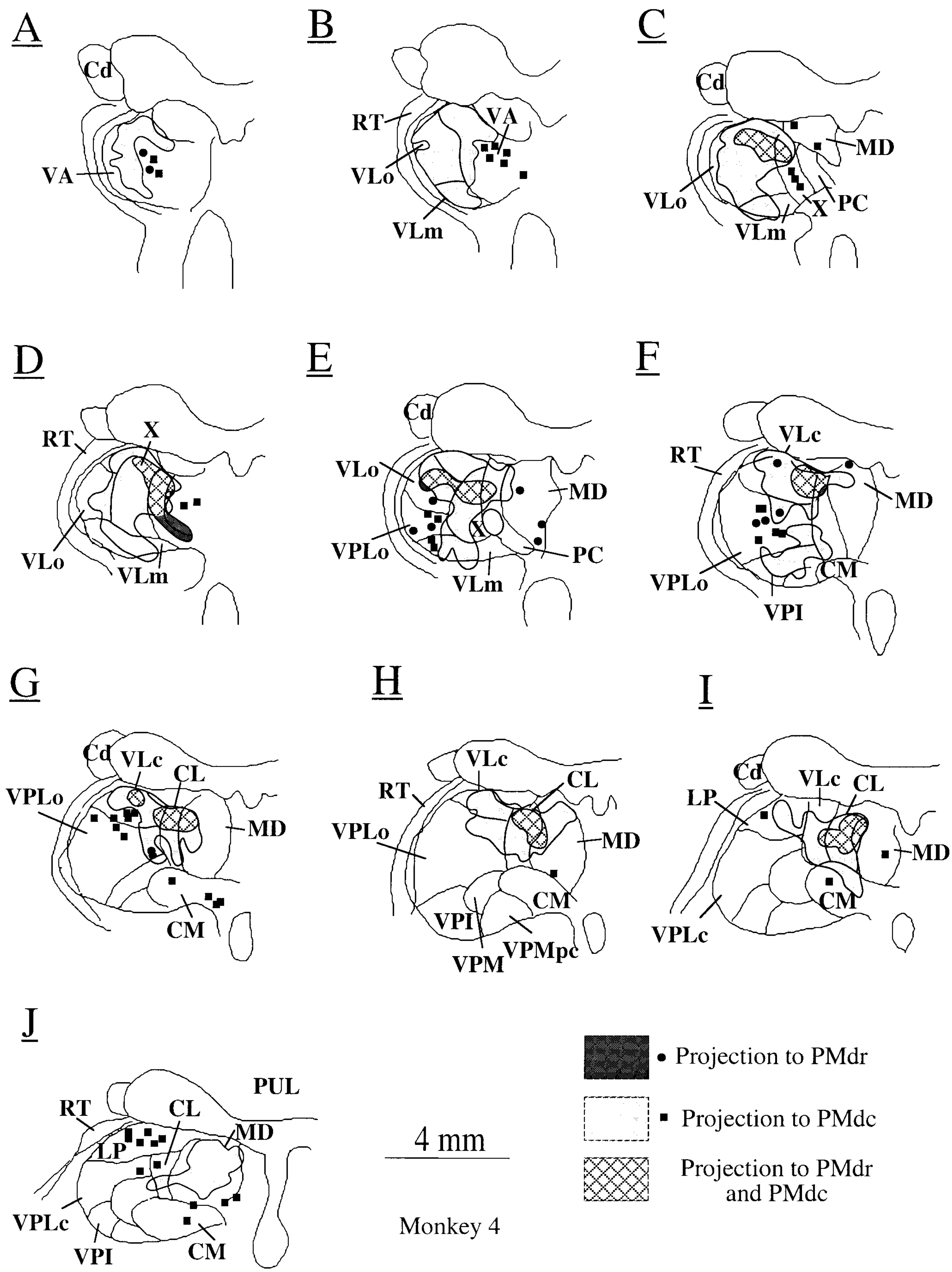

Fig. 9. **A–J:** Spatial distribution in the thalamus of clusters of retrogradely labeled neurons after injections of CB into PMdc and DY into PMdr. Data were derived from monkey 4 (see Table 1). For conventions, see Figure 3. For abbreviations, see list.

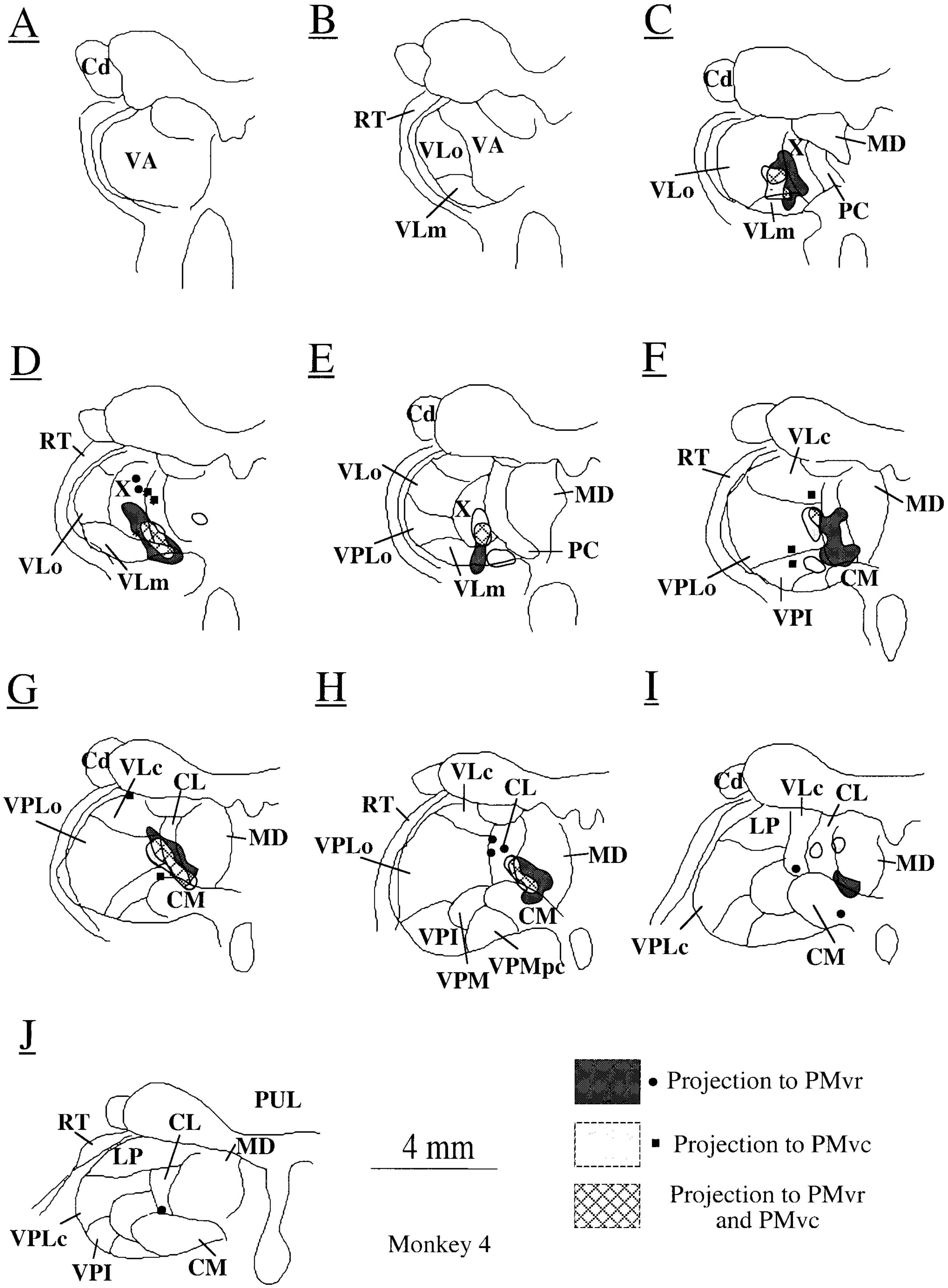

Fig. 10. **A–J:** Spatial distribution in the thalamus of clusters of retrogradely labeled neurons after injections of WGA into PMvc and FB into PMvr. Data were derived from monkey 4 (see Table 1). For conventions, see Figure 3. For abbreviations, see list.

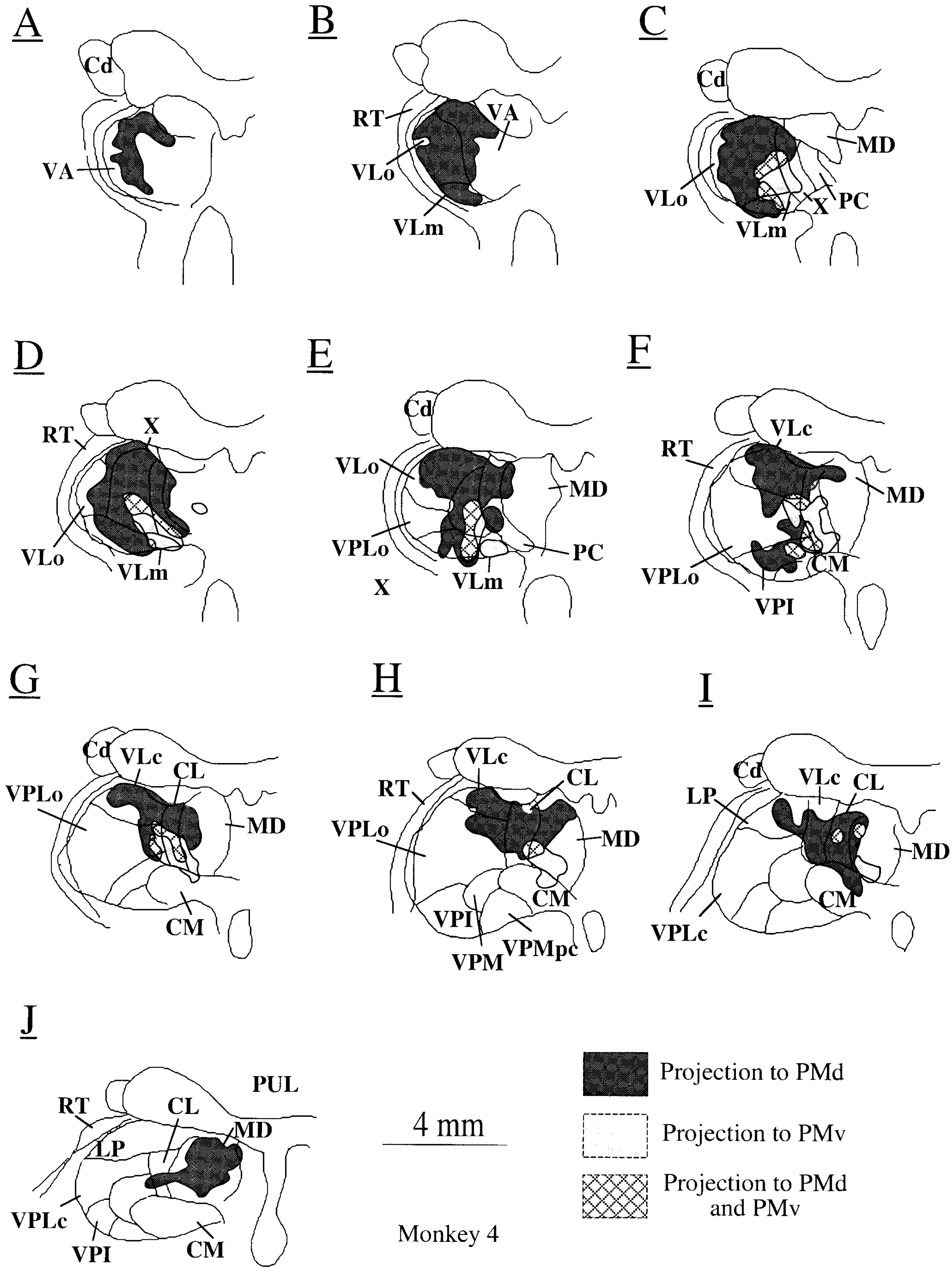

Fig. 11. **A–J:** Combination of the data illustrated in Figures 9 and 10 from monkey 4. This combination shows with different symbols the origin of the thalamocortical projections to PMd (PMdr and/or PMdc) and to PMv (PMvr and/or PMvc), as indicated on the bottom right **inset**. For conventions, see Figure 3. For abbreviations, see list.

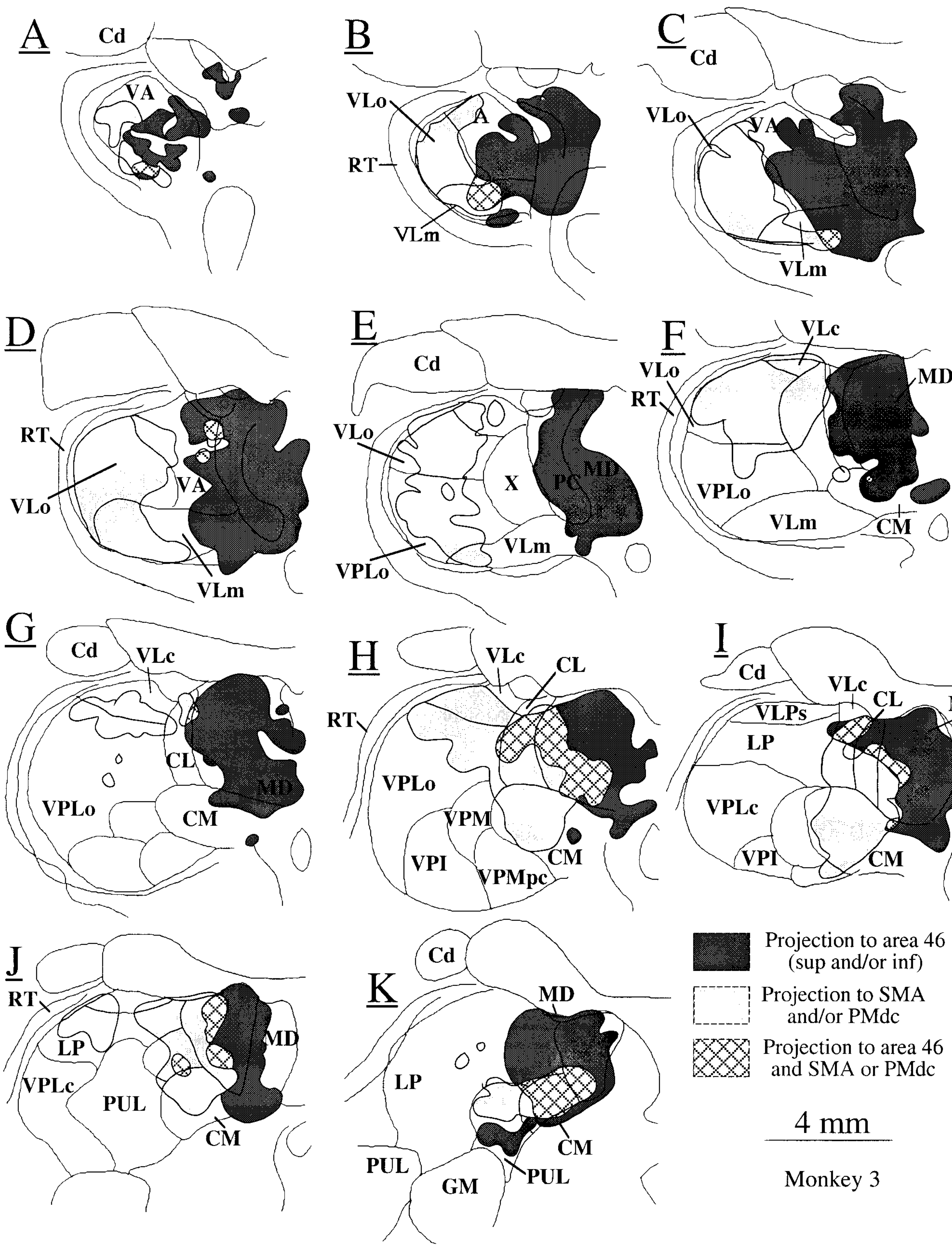

Fig. 12. **A–K:** Combination of the data illustrated in Figures 4 and 5 from monkey 3. This combination shows with different symbols the origin of the thalamocortical projections to PMdc and/or SMA proper on one hand and to area 46 (sup and/or inf) on the other hand, as indicated in the bottom right legend. For conventions, see Figure 3. For abbreviations, see list.

12A,B, in VA and VLo). Farther caudally, they are well separated: The zone projecting to SMA-PMdc clearly is more lateral than the zone projecting to area 46 (Fig. 12D–G). However, in the caudal part of the thalamus, the two territories present a significant degree of overlap in CL and MD (Fig. 12H–K). The thalamic territories projecting to area 46 are even more segregated than those projecting to M1 and PMv (Fig. 13).

DISCUSSION

Thalamocortical projection to M1, SMA, and PM

Figure 14 is a summary of the data indicating the contribution of distinct thalamic nuclei as the origin of the projections directed to M1, SMA, PM, and area 46. Taking the cortical areas individually, the present results are consistent with previous descriptions, most of which were based on single- or double-labeling experiments (compare Fig. 14 with the detailed review above on data available in the literature). The origin of thalamocortical inputs to the hand representation of M1 was established in monkeys 1, 2, and 3 (Table 1) and is illustrated for monkey 3 in Figure 6.

The main sources of inputs to M1 were VPLo and VLo, indicating that our injection sites included parts of both the crest and the sulcus regions (Holsapple et al., 1991). In line with previous observations, retrogradely labeled neurons also were found in VLc and VLm after injection into M1 (Fig. 14).

The origin of the thalamocortical projection to SMA also was determined in monkeys 2 and 3 (Figs. 3, 4, 14). However, these data were applicable only for the microexcitable caudal part of the SMA, referred to as SMA-proper (Matsuzaka et al., 1992) or F3 (Luppino et al., 1993). However, there is recent evidence suggesting that pre-SMA receives inputs from the nuclei VA, area X, MD, and perhaps also VLo (Inase et al., 1996; Matelli and Luppino, 1996; 1996). If this is the case, then pre-SMA and SMA-proper may share a common zone of thalamic inputs in VA, MD, and perhaps VLo. In area X as well as in VA and MD, the territories projecting to pre-SMA may overlap with those directed toward PMd and PMv. Further multiple tracing experiments that include pre-SMA are needed to confirm these speculations. Furthermore, future experiments also should include the three cingulate motor areas, because little is known about the organization of their thalamocortical inputs.

PM is characterized by a large variety of patterns of thalamocortical projections across its different subareas (Fig. 14). For instance, PMdc and PMdr receive considerably different inputs from the thalamus (Figs. 8, 9). However, it is important to emphasize that the thalamocortical connections might vary significantly even within a single cortical area, depending on the precise location of the injections of the tracers. This was the case in the current experiments. In PMdr (compare Fig. 8 with Fig. 9; see also Fig. 1) and in the corresponding F7, the ventral part was found to receive different thalamic inputs than the dorsal part (Matelli and Luppino, 1996).

Thalamocortical projections originating from MD

The present data confirm previous observations that MD is the main thalamic nucleus projecting to area 46 (Goldman-Rakic and Porrino, 1985; Barbas et al., 1991). We observed that the lateral part of MD is also the origin of inputs to SMA-proper and PMdc. This means that the lateral part of MD is a zone of considerable overlap between the clusters of neurons projecting to area 46, SMA-proper, and PMdc. It is noteworthy that this same region of the lateral MD is the target of specialized corticothalamic terminals formed by giant endings coming from SMA-proper and PMdc (Rouiller et al., 1998). This is in contrast with the main corticothalamic projections to VLo and VPLo formed by small endings. The lateral part of MD represents a thalamic zone of particularly dense overlapping input-output connections with the areas SMA-proper, PMdc, and 46. The functional role of these territories of overlapping remains to be elucidated.

Figure 5 shows that the origin of the projections to area 46sup and area 46inf consisted of a limited area mainly in MD projecting to area 46inf, which overlaps completely with a more expanded region (also mainly in MD), giving rise to a projection to area 46sup. This difference in extent of the two territories does not fit with data derived from previous experiments in two separate monkeys but using the same tracer, HRP (see Figs. 9 and 10 in Goldman-Rakic and Porrino, 1985). It is possible that the two tracers used in the present experiment were not equally effective and that the injections may not have been placed in the two studies at comparable rostrocaudal locations.

Summary of data on overlap versus segregation of thalamocortical projections

A significant degree of overlap was obtained in the present study for the thalamocortical projections directed to areas 46sup and 46inf (Fig. 5) as well as for those terminating in SMA-proper and PMdc (Figs. 3, 4). The two subareas of PMv also receive inputs from adjacent and/or common thalamic regions, mainly in area X and VPLo. In contrast, the degree of overlap between M1 and SMA was smaller (Fig. 7). This is in agreement with previous observations of limited overlap of thalamic territories projecting to SMA and to distal and proximal forelimb representations in M1 (Shindo et al., 1995). Similarly, the projection to M1 shares relatively limited zones of origin with the projections directed to PMd (not shown) and PMv (Fig. 6), as reported previously by Kurata (1994). Therefore, M1 appears to receive thalamic inputs that largely are segregated from those directed to the other cortical areas (SMA, PMd, PMv, and area 46). In general, thalamic inputs to the motor cortical areas (M1, SMA, PMd, and PMv) are well segregated from those directed to the prefrontal cortex (area 46; see, e.g., Figs. 12, 13). However, there is one exception: In the lateral region of MD caudally, there was clear overlap of the territories sending projections to area 46, SMA-proper, and PMdc (Figs. 3, 4, 12). After injections of FB and DY, several multiple-tracing studies (including the present one) converge to suggest that very few neurons were double labeled. In other words, there are no thalamocortical projections to several cortical areas that originate from an individual neuron. On the contrary, they originate from distinct thalamic neurons; however, in the zones of overlap, the neurons with different destinations can be intermixed.

Technical limitations

The present data apply to a restricted zone of cortical areas, in particular, to M1, SMA, and PMdc, where ICMS

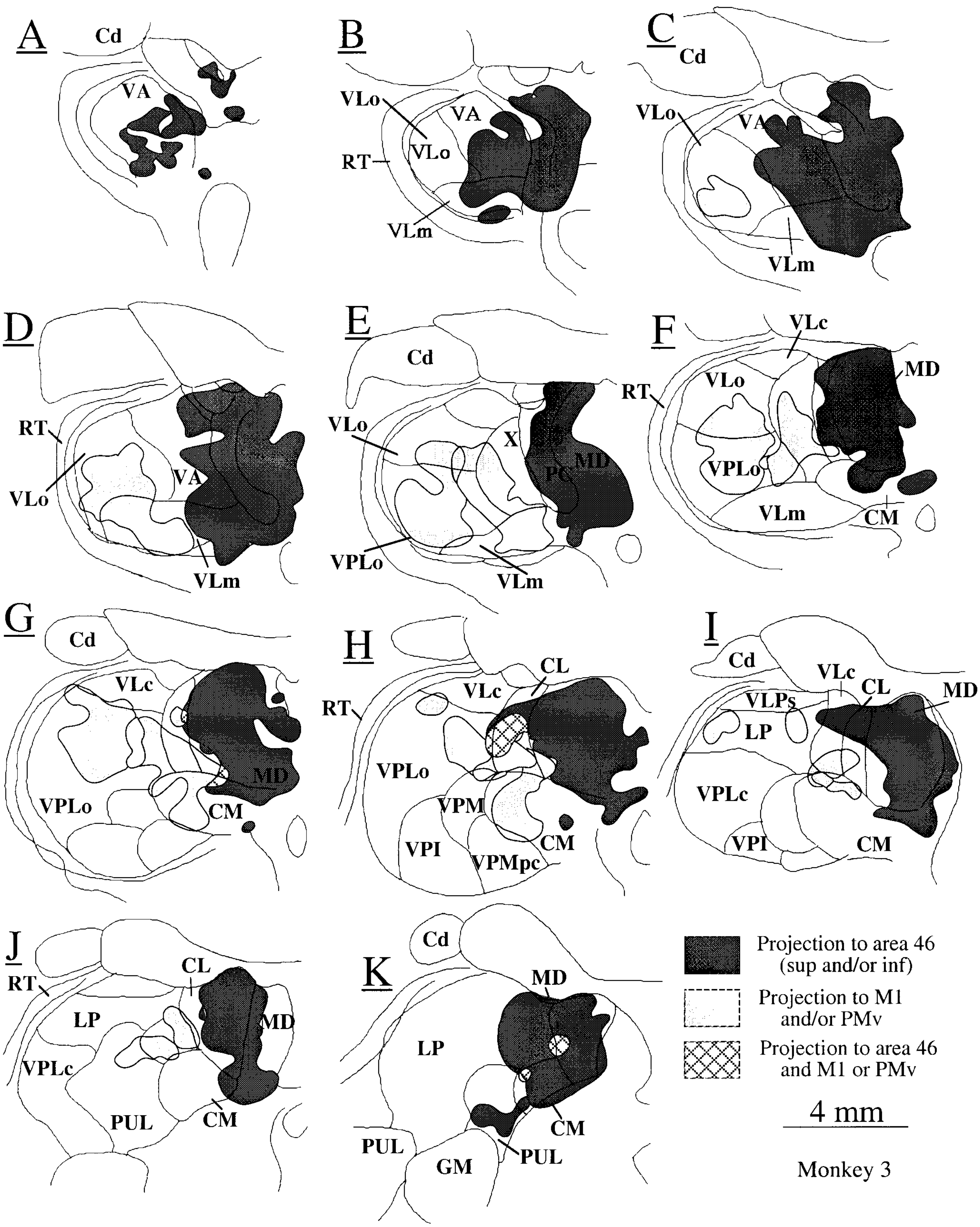

Fig. 13. **A–K:** Combination of the data illustrated in Figures 5 and 6 from monkey 3. This combination shows with different symbols the origin of the thalamocortical projections to M1 and/or PMv on one hand and to area 46 (sup and/or inf) on the other hand, as indicated on the bottom right **inset**. For conventions, see Figure 3. For abbreviations, see list.

and single-unit recordings were used to guide the injections into the hand/arm representation. Therefore, one cannot extend the present observations to other parts of the somatotopic map, such as the face or the hindlimb. Along the same lines, the present observations also are limited by the less systematic and precise electrophysiological guidance of the injection sites in other cortical areas (PMdr, PMv, area 46). In these areas, the injection sites might not ideally match somatotopically those performed in M1, SMA-proper, and PMdc.

The interpretation of the present data is also limited by other technical difficulties. The number of areas that could be investigated in an individual monkey was limited by the number of sufficiently reliable retrograde tracers available. In addition, these tracers may vary with respect to sensitivity, selectivity of uptake, velocity of transport, diffusion from the injection site, etc. Moreover, delineation of the injection site was easier for some tracers (e.g., FB, DY, BDA) than for others. In particular, delineation of the diffusion zone for WGA and CB could not be estimated with precision. Consequently, comparison across cortical areas is affected by such differences. We tentatively switched the tracers around from one monkey to the next (Table 1) to take into account these parameters. Although some tracers could be visualized on the same individual section (the fluorescent tracers), the nonfluorescent tracers were visualized on adjacent sections. This introduces an uncertainty when plotting the clusters of retrogradely labeled neurons on a common reconstruction. All of these factors, but mainly the precise location of the injections and the tracers' characteristics, can contribute to differences across monkeys for the distribution of retrograde labeling in the thalamus after tracer injection into a given cortical area. An example of the effect of the precise location of the injection sites may be the discrepancy between monkeys 4 and 5 with respect to the projections directed to PMdr and PMdc (see Results; compare Fig. 8 with Fig. 9), although different tracer characteristics (more labeling obtained with CB than DY, at least for the volumes injected here; see Table 1) also may play a role.

Grouping of cortical areas based on their thalamocortical connectivity

The multiple motor areas have been grouped on the basis of their pattern of inputs coming from the thalamus (Fig. 14). For instance, SMA-proper and PMdc were combined to reflect the comparable organization of their thalamic inputs, in particular with VLo as the main source of projections. In addition, SMA-proper and PMdc exhibit a similar pattern of corticothalamic projections (Rouiller et al., 1998). M1 was placed in a separate group, because it clearly differs from SMA-proper and PMdc for the organization of both the corticothalamic (Rouiller et al., 1998) and thalamocortical projections. M1 also clearly contains more corticospinal neurons than any other motor cortical area (Dum and Strick, 1991). The present results show

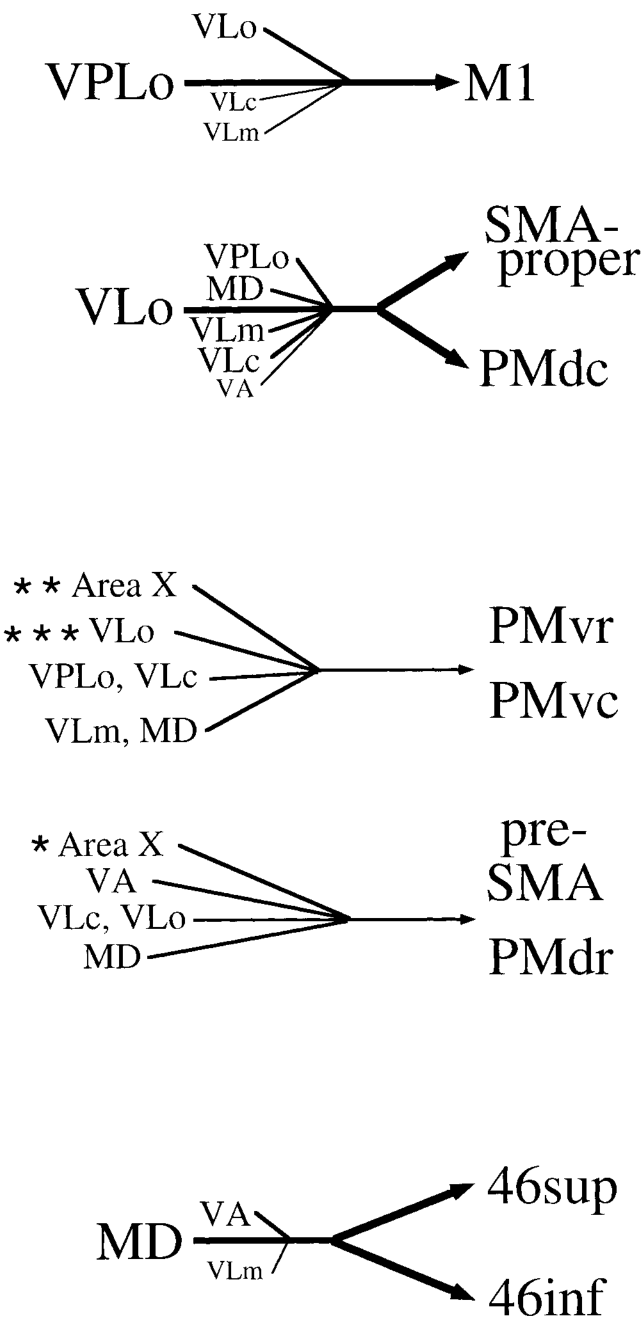

Fig. 14. Simplified representation of the data, indicating the thalamic nuclei giving rise to a projection to the cortical areas included in the present study. Based on the set of thalamic nuclei giving rise to their thalamocortical projections, the cortical areas were distributed into five groups (right column; see Discussion). The left column represents the thalamic nuclei of origin of the projections reaching the various cortical areas. Where a main thalamic nucleus of origin is well defined, it is indicated in large letters, whereas, in the absence of such a clear predominance, the nuclei of origin are listed by using the same medium-sized or small letters. The density of the corresponding projection is indicated by the thickness of the projection arrows (thick, medium, thin) and by the letter size of the thalamic nuclei (large, medium, small). Pre-SMA was added to this figure based on data available in the literature, because no injection into pre-SMA was performed in the present study. Also, for clarity, no data regarding the thalamic nuclei CL, CM, PC, VPI, VPM, or LP have been represented here. For two groups of cortical areas (SMA-proper and PMdc; areas 46sup and 46inf), the arrow diverged to indicate a substantial amount of overlapping of the projections directed to the two cortical areas. Asterisks indicate a trend for the corresponding thalamic nuclei to give a slightly denser projection than the other nuclei to the areas PMdr (single asterisk), PMvr (double asterisks), and PMvc (triple asterisks).

that M1 receives inputs mainly from VPLo, and it has limited overlap with the thalamic territories projecting to the other cortical areas (area 46, SMA, PM). Area 46 (both 46sup and 46inf) can be distinguished clearly from other cortical areas on the basis of their main thalamic inputs originating from MD. Finally, the four remaining motor areas were considered separately, because they did not receive a clearly predominant input from a given thalamic nucleus. Pre-SMA and PMdr were grouped together, because they exhibited fairly common properties with respect to their thalamic inputs (in particular, inputs coming from VA, but not from VPLo and VLm, in contrast to PMvr and PMvc). This segregation (pre-SMA and PMdr separated from PMvr and PMvc) is consistent with the notion that pre-SMA and PMdr both lack corticospinal neurons and lack interconnections with M1, in contrast to PMvr and PMvc, as well as SMA-proper (see, e.g., Dum and Strick, 1991; Kurata, 1991; Luppino et al., 1993; Rouiller et al., 1994b; Gosh and Gattera, 1995). However, it is important to emphasize that such categorization should not be taken strictly with abrupt separation between groups. Rather, one might favor a progressive transition between grouping, with properties progressively changing from one group to another. This view is consistent with observations that almost all types of neurons characterized electrophysiologically in relation to a given motor task are present in all areas but in different proportions (see, e.g., Alexander and Crutcher, 1990a,b; Crutcher and Alexander, 1990; Chen et al., 1991; Halsband et al., 1994; Kermadi and Boussaoud, 1995; Tanné et al., 1995; Matsuzaka and Tanji, 1996; Kermadi et al., 1998), in line with the idea of progressive rather than abrupt transitions from one area to the next. The same appears to be true for the connectivity. The patterns of thalamocortical projections appear to change more progressively than abruptly when considering different cortical areas. The results of the present study further indicate that the origin of thalamic inputs to the cortex transgresses cytoarchitectonic borders and that each area receives weighted inputs from several distinct thalamic nuclei (see Darian-Smith et al., 1990).

ACKNOWLEDGMENTS

The authors thank N. Zeller-Boyer for excellent technical assistance and M.-L. Loyalle, J. Corpataux, and B. Morandi for animal care. We thank Dr. H.C. Cromwell and Dr. S. Waxman for editorial comments. The present work was supported by the Swiss National Science Foundation (grants No 3130–025138, 31–28572.90, 31–43422.95 to E.M.R.).

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