THE JOURNAL OF COMPARATIVE NEUROLOGY 319:123–140 (1992)

The Somatosensory Thalamus of Monkeys: Cortical Connections and a Redefinition of Nuclei in Marmosets

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ABSTRACT

Thalamic connections of three subdivisions of somatosensory cortex in marmosets were determined by placing wheatgerm agglutinin conjugated with horseradish peroxidase and fluorescent dyes as tracers into electrophysiologically identified sites in S-I (area 3b), S-II, and the parietal ventral area, PV. The relation of the resulting patterns of transported label to the cytoarchitecture and cytochrome oxidase architecture of the thalamus lead to three major conclusions. 1) The region traditionally described as the ventroposterior nucleus (VP) is a composite of VP proper and parts of the ventroposterior inferior nucleus (VPi). Much of the VP region consists of groups of densely stained, closely packed neurons that project to S-I. VPi includes a ventral oval of pale, less densely packed neurons and finger-like protrusions that extend into VP proper and separate clusters of VP neurons related to different body parts. Neurons in both parts of VPi project to S-II rather than S-I. Connection patterns indicate that the proper and the embedded parts of VPi combine to form a body representation paralleling that in VP. 2) VPi also provides the major thalamic input into PV. 3) In architecture, location, and cortical connections, the region traditionally described as the anterior pulvinar (AP) of monkeys resembles the medial posterior nucleus, Pom, of other mammals and we propose that all or most of AP is homologous to Pom. AP caps VP dorsomedially, has neurons that are moderately dense in Nissl staining, and reacts moderately in CO preparations. AP neurons project to S-I, S-II, and PV in somatotopic patterns.

Key words: parietal ventral area, S-I, S-II, ventroposterior nucleus, ventroposterior inferior nucleus

In the present study, we describe thalamic connections of three subdivisions of somatosensory cortex of primates. The major thalamic connections of one subdivision, area 3b or S-I proper (Kaas, '83) seem well established. As for S-I in other mammals, major activating inputs of area 3b in monkeys and prosimians are from the ventroposterior nucleus, VP, and the inputs form a topographic pattern (e.g., Lin et al., '79; Nelson and Kaas, '81; Jones and Friedman, '82; Jones et al., '82; Kaas, '82; Cusick et al., '85; Mayner and Kaas, '86; Cusick and Gould, '90). However, such connection patterns have not been described for marmosets or other callitrichines. In addition there is little information on the full extent of VP and other thalamic zones projecting to S-I in primates and other mammals. Thus, we injected tracers in several different locations in area 3b of each case, filling much of the body representation.

Other injections were placed in S-II. Traditionally, the major source of thalamic input to S-II in both primates and other mammals is reported to be from the ventroposterior nucleus (e.g., Macchi et al., '59; Jones and Powell, '69; Burton and Jones, '76; Jones and Powell, '70). Results from more recent studies support the conclusion that VP projects densely to both SI and SII in a number of nonprimate mammals (see Krubitzer and Kaas, '87), and in cats, at least, it appears from a double labeling study (Spreafico et al., '81) that some of the neurons in VP project to both S-I and S-II. Thus, VP does seem to be the major source of thalamic input to S-II in some mammals, as originally postulated as a general principle. However, the possibility that the source of the major thalamic input to S-II may be species variable was suggested by Herron ('83) who demonstrated that most of the neurons projecting to S-II in raccoons are in the ventroposterior inferior nucleus, VPi, rather than in VP. In macaque monkeys, Friedman et al. ('83) also reported that the major source of inputs to S-II was VPi rather than VP (see Friedman and Murray, '86 for a full report). Data published by Manzoni et al. ('84) seemed to confirm this conclusion. However, Burton ('84) described

Accepted January 21, 1992.

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corticothalamic projections from S-II to both VP and VPi in macaque monkeys and urged caution in concluding VPi provides the primary relay to S-II in primates. More recently, Burton and Carlson ('86) described projections to S-II in the prosimian primate, galago, as originating from neurons in both VP and VPi. Because of these proposed differences, we examined the thalamic connections of S-II in marmosets, a primate where it is relatively easy to access S-II and electrophysiologically define its extent. We specifically addressed the issue of whether neurons projecting to S-II are located in VPi, VP, or both.

Our study, of course, involved defining and distinguishing subdivisions of the ventroposterior complex. VPi is a curious subdivision of the thalamus in that there have been few attempts to define this nucleus in non-primate mammals (see Jones, '85 for review). The nucleus consists of an oval of small, pale-staining cells just ventral to VP in monkeys (e.g., Dykes et al., '81) and raccoons (Herron, '83), but a nucleus of comparable size and architecture is not apparent in most mammals (Krubitzer and Kaas, '87). After reviewing previous descriptions, Jones ('85) concluded that VPi is evident only in primates, and that even in primates VPi is not a well-defined entity. VPi has been characterized as a source of projections to dysgranular insular cortex (Roberts and Akert, '63; Burton and Jones, '76) as well as S-II (Friedman and Murray, '86). In this report, we describe VPi in both standard Nissl preparations and in brain sections processed for cytochrome oxidase. The results permit a clearer distinction between VPi and VP, and also suggest that parts of VPi extend dorsally into VP and are embedded within and around VP. This distinction is important in our interpretation of the cortical connections of VPi and VP.

A final goal was to determine the thalamic connections of PV. The parietal ventral area, PV, is defined by a systematic representation of the body surface first described in squirrels (Krubitzer et al., '86) and subsequently in other rodents (Li et al., '90; Fabri et al., '90; however, see Koralek et al., '90) and megachiropterian bats (Krubitzer and Calford, '92). We recently described the body surface map, architecture, and cortical connections of PV in marmosets (Krubitzer and Kaas, '90). In rodents, bats and primates, PV is located along the lateral border of S-I, just rostrolateral to S-II, and PV has major inputs from both S-II and S-I. In marmosets, PV is located in granular cortex of the lateral fissure in the region of granular insular cortex of macaque monkeys (see Friedman et al., '86). In squirrels, the major thalamic input to PV, like S-II, is from VP (Krubitzer and Kaas, '87), but, as a newly defined subdivision of somatosensory cortex, thalamic connections of PV have not yet been described in primates. However, there is evidence that cortex in the region of PV receives inputs from VPi and the suprageniculate nucleus (Burton and Jones, '76).

Marmosets were used in the present studies largely because their small, smooth brains offered clear technical advantages in mapping, placing injections, and flattening cortex. Marmosets were also of interest because it is important to determine similarities and differences across the major branches of primates evolution, and the callitrichines (marmosets and tamarins) are the smallest and most distinctive New World monkeys (Fleagle, '88) with several primitive characteristics (see Carlson et al., '86). Some of the present results have been briefly presented elsewhere (Kaas and Krubitzer, '90).

MATERIALS AND METHODS

The thalamic connections of 3b, S-II, and the parietal ventral area, PV were examined in 8 marmoset monkeys (*Callithrix jacchus*) by placing small amounts of anatomical tracers into electrophysiologically defined representations of body parts in each field as previously described (Krubitzer and Kaas, '90). Thalamic connections of these cortical fields were determined by relating transported tracer to architectonic subdivisions of the thalamus. Architectonic subdivisions of the thalamus were delimited in brain sections stained for Nissl substance or treated for cytochrome oxidase. Experiments were of three types. First, multiple injections of wheatgerm agglutinin conjugated with horseradish peroxidase (WGA-HRP) were closely spaced within the electrophysiologically identified boundaries of 3b. We reasoned that by filling most of a cortical field, we could fill almost an entire thalamic nucleus with transported tracer and use the limits of the transported tracer to help determine the full extent of the thalamic nucleus. In the second set of experiments, different anatomical tracers were placed into different body part representations of the same field so that the transported tracer would reveal the topography of thalamic nuclei. Finally, different anatomical tracers were placed into the same body part representation of different cortical fields allowing similarities and differences of thalamic connections of different fields to be directly assessed.

Surgery

At the beginning of each experiment, the animal was anesthetized with ketamine hydrochloride (30 mg/kg) and acepromazine (1 mg/kg IM). Approximately half of this initial dose of both ketamine and acepromazine was given as needed throughout surgery to maintain a surgical level of anesthesia. A local anesthetic, 2% xylocaine hydrochloride, was injected subcutaneously in the scalp and the ear canals. Using standard sterile surgical procedures, the scalp was cut and retracted, the skull was removed above the somatosensory cortex, and dura was retracted. A small acrylic well was built around the opening in the skull and filled with silicone fluid. An enlarged photograph of the brain was made so that electrophysiological recording sites could be marked in relation to the cortical vasculature. When electrophysiological recordings and microinjections were complete, the acrylic well was removed, the dura was sutured and the bone flap was replaced. The skin was sutured and the animals were allowed a survival time of 2–3 days.

Recordings

Using low impedance (0.95–1.5 M Ω at 1 KH_z) tungsten microelectrodes, we recorded from neural clusters approximately 700 μ below the pial surface in the middle layers of cortex. A micromanipulator moved the electrode in X/Y coordinates and a stepping microdrive advanced the electrode through the cortical layers. In area 3b, electrode penetrations were perpendicular to the cortical surface. In S-II and PV, the electrode was advanced down the dorsal bank of the lateral sulcus, parallel to cortical layers, and recordings were obtained from neurons in electrode penetrations running parallel to and through layer IV. Penetrations were typically placed about 0.5 mm apart, and recordings were made every 200–300 μ along the penetration. By lightly tapping the skin with glass probes, displacing hairs, brushing the skin with fine brushes, directing gentle puffs

of air on the skin surface, or applying deep pressure, receptive fields for neurons at various recording sites were determined and drawn on pictures of the body. Physiological boundaries of cortical fields were marked with small electrolytic lesions (10 μ amps for 6 seconds) so that physiological results could later be related to patterns of transported tracer and cortical myeloarchitecture.

Injections and histology

Micropipettes coupled with a Hamilton syringe were used to inject small amounts of anatomical tracers into electrophysiologically identified body parts in the cortical area of interest. Anatomical tracers included WGA-HRP, tritiated WGA (see Steindler and Bradley, '83), and the fluorescent dyes, fast blue, diamidino yellow, and fluoro-gold. Each injection consisted of .03–.05 μl of 1% WGA-HRP or ^{3}H-WGA (1.98 mCi/mg.) or .2–.4 μl of 2–4% fluorescent dye. After the appropriate survival time, 48 hours for WGA and 72 hours for fluorescent dyes, each animal was administered a lethal dose of sodium thiopental and transcardially perfused with 0.9% saline followed by 2% paraformaldehyde in phosphate buffer and then 2% paraformaldehyde in 10% sucrose phosphate buffer. The cortex was separated from the brainstem and thalamus and flattened between glass slides. Both the cortex and thalamus were soaked overnight in 30% sugar phosphate buffer, frozen, and sectioned at 40 or 50 μ. The cortex was sectioned parallel to the cortical surface and the thalamus was sectioned coronally. Alternate sections of the thalamus were processed for HRP with tetramethylbenzidine (Mesulum, '78), mounted for fluorescent microscopy, processed for cytochrome oxidase (CO; Wong-Riley, '79), or stained for Nissl substance. In the case where tritiated WGA-HRP was injected, a series of sections was mounted for autoradiography. Sections were processed for autoradiography according to procedures outlined by Cowan et al. ('72). Coated sections were exposed for nine weeks at 4°C in the dark, developed, and stained with cresyl violet. Details of cortical histology are presented elsewhere (Krubitzer and Kaas, '90).

Data analysis

With the aid of a camera lucida, enlarged drawings of both the cortex and thalamus were made that included anterogradely labeled axon terminals, retrogradely labeled cell bodies, and relevant blood vessels and tissue artifacts. In the WGA-HRP material, dense label within cell soma marking retrogradely labelled neurons could be easily distinguished from fine, powder-like distributions of label outside of soma, which was assumed to be largely anterogradely labeled axon terminals. By aligning blood vessels in brain sections containing transported tracer with adjacent sections stained for Nissl substance or processed for CO, thalamic architectonic boundaries could be added and related to patterns of transported tracer. In the cortex, architectonic boundaries were determined in a similar manner and electrophysiological lesions were identified so that cortical injections were related to both architecture and physiological boundaries. All injections were confined to the cortical field of interest. Cortical connections of somatosensory fields have been reported previously (Krubitzer and Kaas, '90).

RESULTS

Architectonic subdivisions of the ventroposterior thalamus

Photographs of brain sections stained for cell bodies (Nissl) or processed for cytochrome oxidase (CO) illustrate several features of thalamic architecture (Figs. 1, 2) that relate to patterns of cortical connections. First, VP and VPi are easily distinguished by a sharp contrast in appearance. VP contains groups and larger blocks of densely packed and darkly stained neurons, and these regions react densely for CO. In contrast, VPi consists of neurons that appear to be less densely stained, smaller, and less densely packed. The VPi region is much less dense than VP in expressed CO. These distinctions conform to previous descriptions based on Nissl preparations from other New World monkeys (see Emmers and Akert, '63; Dykes et al., '81; Kaas et al., '84; Cusick et al., '85; Cusick and Gould, '90) and Old World monkeys (see Jones, '85), and descriptions of differences in CO reactivity (Cusick and Gould, '90; Jones et al., '86a,b; Rausell and Jones, '91a).

A second relevant feature of thalamic architecture is that fingers of VPi extend up into VP (Figs. 1, 2). This feature of VPi and VP is especially obvious in CO preparations, but it is also apparent in Nissl stained sections. Like VPi, the inserted regions in VP have pale staining, less densely packed, small neurons, and these regions react lightly for CO. The inserted regions have been described previously, especially those separating face, hand, and foot subnuclei of VP (see Kaas et al., '84, for review), and more recently for the separations of representations of subdivisions of the face (Jones et al., '86a,b), and digits and other parts of the body (Cusick and Gould, '90). In the small brains of marmosets, the CO light zones inserted in VP appear to be proportionately larger than in the relatively larger brains of cebid and catarrhine monkeys. The CO light regions are larger in rostral and caudal extremes of VP and they may even partially cap VP (Fig. 3). The overall appearance from the Nissl and CO patterns is that VPi protrudes into and around VP, but the larger part of VPi is ventral to VP (Fig. 3). By surrounding VP, VPi somewhat resembles in topography the "shell" region that has been described for VP (e.g., Jones and Friedman, '82). The more medial protrusions of VPi into VP appear to correspond to parts of the medial "nucleus" of VPi that Rausell and Jones ('91a,b) refer to as the "background matrix domain" in macaque monkeys.

A third notable aspect of thalamic architecture is that two separate capping nuclei are distinguishable along the dorsal border of VP. The more medial of these is the anterior pulvinar, AP, of monkeys and hominoids (see Jones, '85). This thalamic structure is characterized by less densely packed neurons and an overall lighter appearance than VP in Nissl and CO preparations. In other mammals, AP has not been recognized as such. For example, in prosimians, AP apparently has been included in the posterior group by Burton and Carlson, '86. In rodents and cats, the medial posterior nucleus, POM, appears by position and connections (see Krubitzer and Kaas, '87) to be the homologue of AP. The other more lateral capping nucleus is the ventroposterior superior nucleus, VPs, that has somewhat reduced cell packing and CO density than VP. VPs is a recently distinguished subdivision of the ventroposterior complex (see Diamond, '82) that has most dense connections with areas 3a and 2 in other species of monkeys, (Kaas et al., '84; Cusick et al., '85; Pons and Kaas, '85; Cusick and Gould, '90).

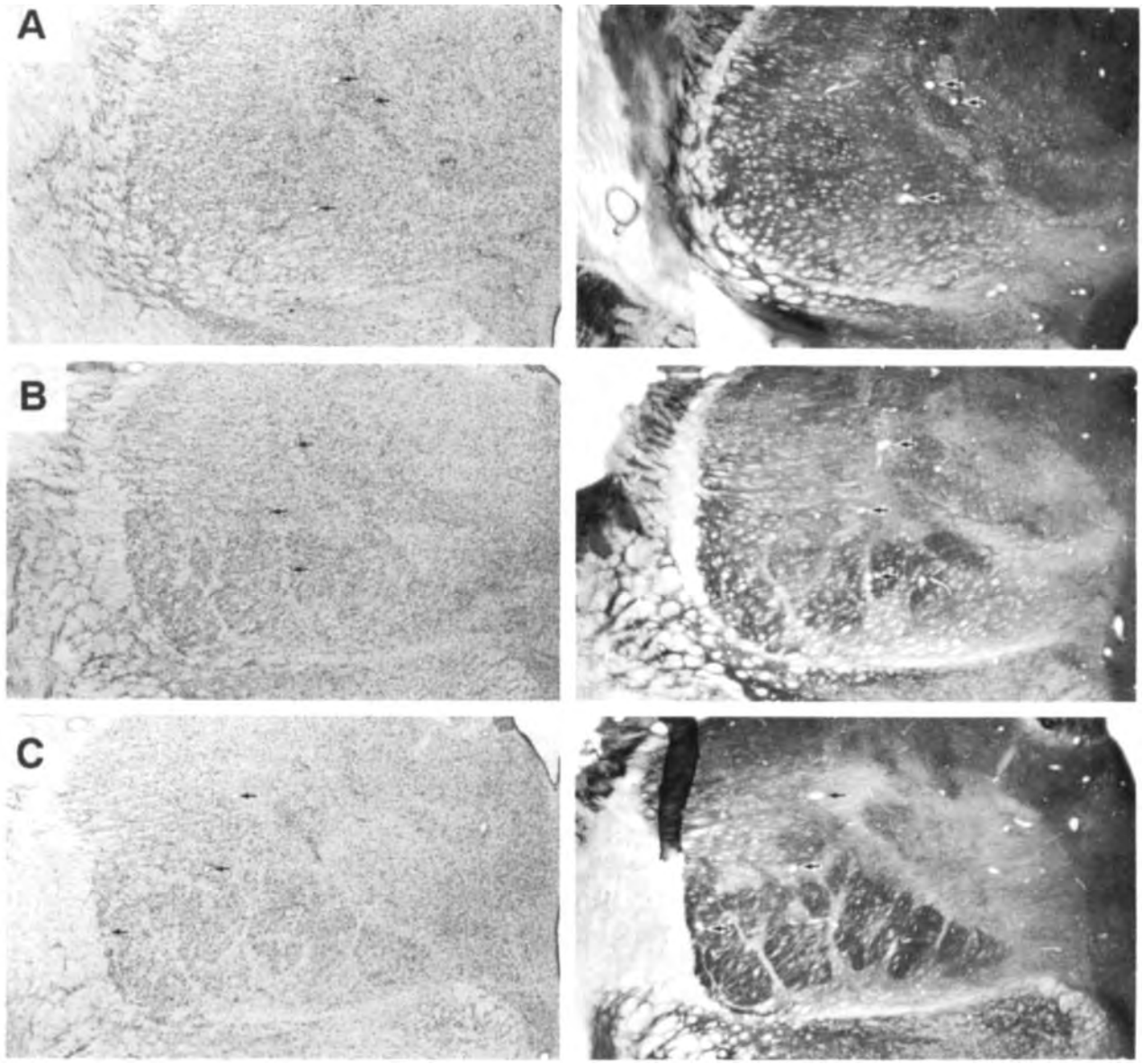


Fig. 1. Lightfield photomicrographs of adjacent thalamic sections that have been stained for Nissl substance (left) or processed for cytochrome oxidase (right). In this case, the thalamus was sectioned at 40 μm and the rostrocaudal series of pairs of coronal sections (**A, B,** and **C**) are 160 μm apart. Arrows in adjacent sections mark the same blood vessels that can be superimposed to align sections. The ventral posterior nucleus (VP) contains densely packed and darkly staining neurons. In sections processed for cytochrome oxidase, VP stains very darkly and is separated by very lightly staining extensions of the ventral posterior inferior nucleus (VPi). The largest portion of VPi is located ventrally, but finger-like projections also extend into VP. A very thin cytochrome oxidase (CO) light region is also found dorsally and may be included as a portion of VPi. In this and the following figures, medial is to the right and dorsal is to the top. See Figure 2 for scale bar.

Connections of area 3b

Injections of tracers were placed with electrophysiological guidance (see Krubitzer and Kaas, '90) in area 3b with three goals in mind. In two animals, our goal was to place multiple injections of a single tracer in a mediolateral sequence in order to involve most of the portion of 3b that represents the body. Because of time limitations and other practical considerations, the rostrolateral part of area 3b representing the teeth and other parts of the mouth were not fully mapped and injected. Thus, the cases do not provide evidence on the complete extents of thalamic structures projecting to area 3b. Nevertheless they do indicate the extents of the portions of nuclei projecting to the part of 3b representing the body rather than the head. In one case, different tracers were put in three locations in area 3b, each devoted to a separate body region, in order to determine the somatotopy of nuclei projecting to area 3b. In a third type of experiment, injections of different tracers were placed in the representations of similar body parts in 3b and S-II to determine if neurons in similar or different locations project to the two targets.

In each of the two cases with mediolateral rows of WGA-HRP injections in area 3b, most of the label was in the ventroposterior nucleus. Figure 4 shows a mixture

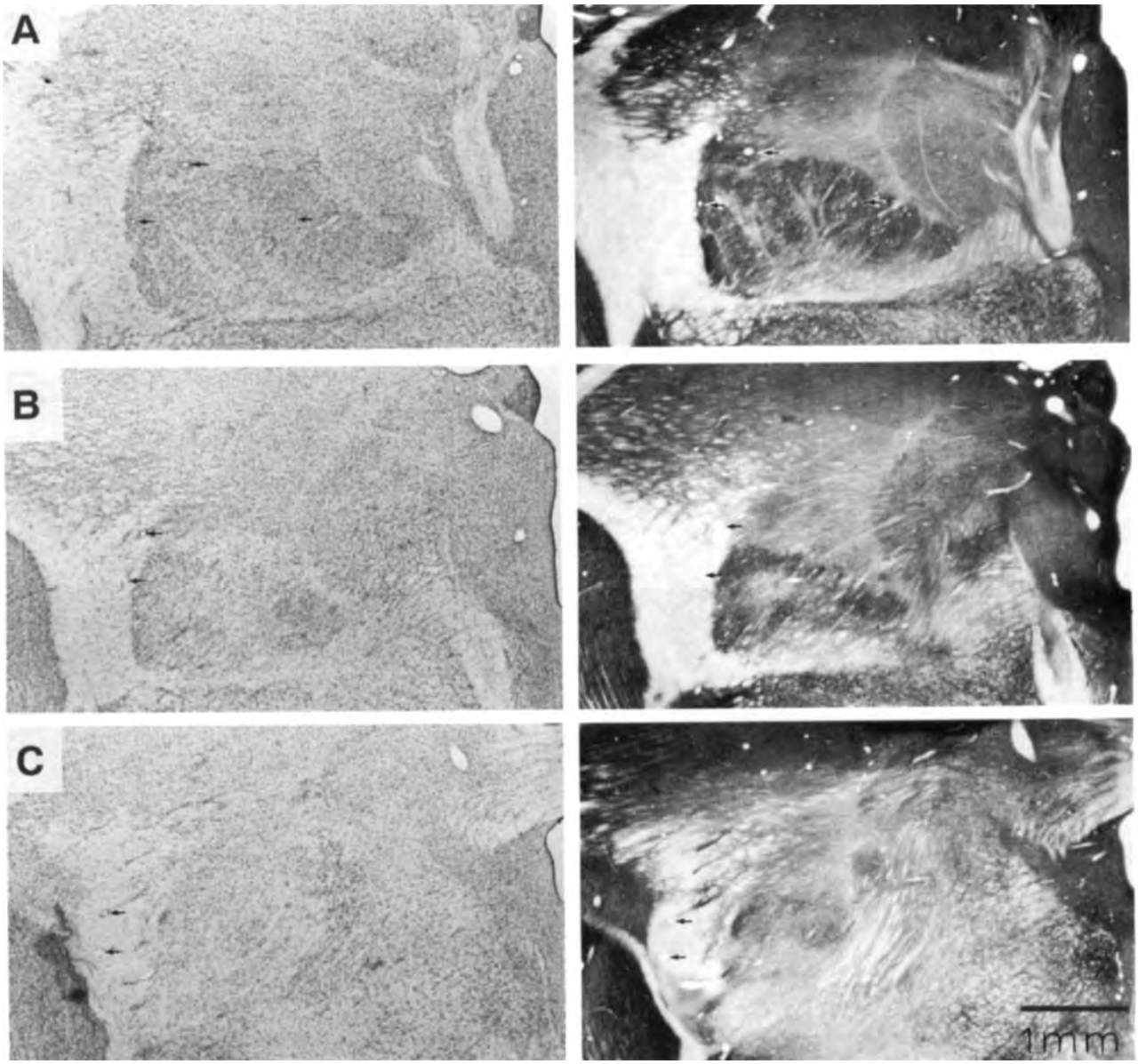


Fig. 2. A caudalward continuation of the series of thalamic sections of Figure 1. Sections 2A are 160 μm caudal to those of 1C.

of retrograde and anterograde label in part of a brain section through VP of case 85-26, and the adjacent section reacted for CO clearly shows both the extent of VP and the CO light regions that parcellate VP. Note that the label, including neurons and the presumed corticothalamic terminals, was concentrated within VP proper, rather than the inserted CO light regions. Some dense label was also dorsal to VP in the anterior pulvinar. VPi was almost totally free of label.

Results from case 85-26 are more comprehensively summarized in Figure 5. The most important observation is that throughout the VP region, labeled neurons and axon terminals were almost exclusively confined to the densely packed cell clusters of VP rather than the cell-sparse regions of embedded VPi. Some sparse, scattered label was observed in embedded VPi and in VPi proper, but this label could reflect fibers of passage as well as terminals. A few labeled cell bodies were found in both parts of VPi. Moderate amounts of label were also present in AP, sparse amounts were in VPs, and a few labeled neurons were in the interlaminar nuclei. Results from the other case with mediolateral rows of injection sites in area 3b were similar to those from case 85-26. In case 85-29 (not shown), a number of closely spaced injections were confined to 3b and fused together to form a single strip injection that encompassed representations of the foot, hindlimb, trunk, forelimb, hand, and head. Transported tracer was concentrated predominately in VP and formed clumps that related to separate body parts in this nucleus. No label was noted in VPm. Moderate amounts of label were in VPs and AP, and sparse patches of transported tracer were in VPi, CM and Pc. Thus, the thalamic connections revealed in both cases that had strip injections of WGA-HRP encompassing most of the mediolateral extent of 3b were very similar.

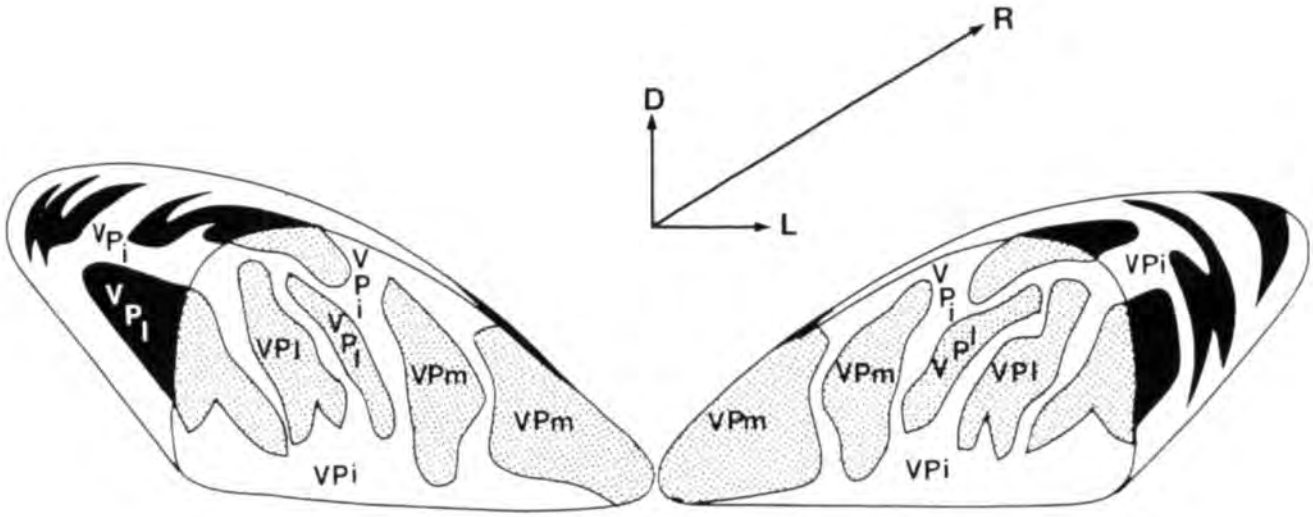


Fig. 3. A schematic of the relationship of medial (VPm) and lateral (VPl) subdivisions of the ventroposterior nucleus (VP) to the ventroposterior inferior nucleus VPi. VP is more continuous in the rostrocaudal plane but highly disrupted in the mediolateral plane. VP is separated by the finger-like projections of VPi. VPi almost completely encapsulates VP. Dorsal (D), lateral (L), and rostral (R) directions are indicated.

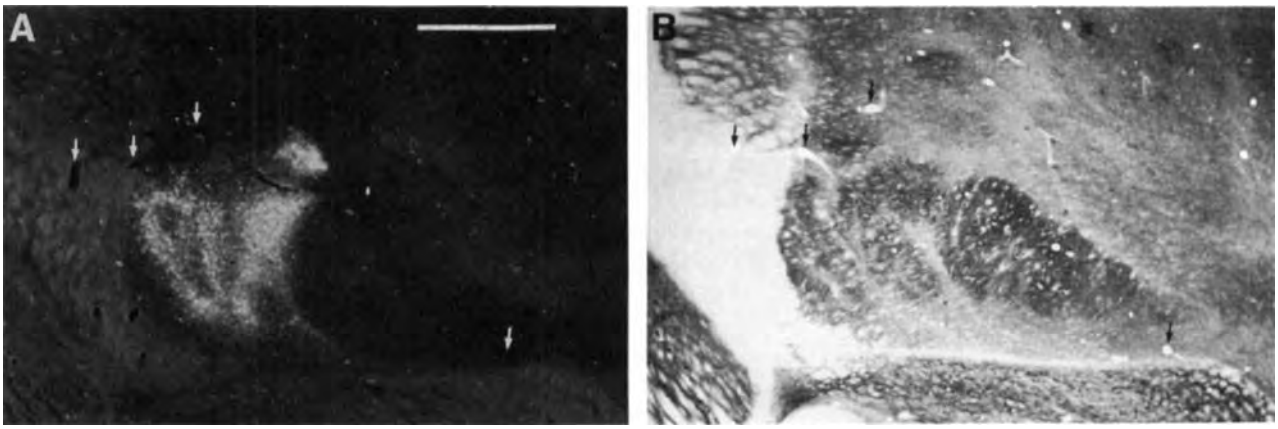


Fig. 4. **A:** A darkfield photomicrograph of an HRP treated brain section showing the distribution of anterograde and retrograde label in VPl after a strip of injections of WGA-HRP in area 3b. Lateral is left in this coronal brain section through the somatosensory thalamus. **B:** An adjacent section processed for cytochrome oxidase, CO. The label in A is found predominantly in the CO dense patches that compose VP. The patch of label dorsal to VP is in the anterior pulvinar. Arrows point to the same blood vessels in A and B. Case 85-26. Compare with Figure 5. Scale bar, 1 mm.

Aspects of the somatotopic organization of VP were revealed in two cases where two or three different tracers were injected into the representations of different body parts in 3b. In case 86-51, three tracers were placed in a mediolateral sequence in area 3b (Fig. 6). The middle injection, placed in cortex responsive to stimuli on the digits of the hand, labeled neurons and axons ventrally in VP proper in a region corresponding to the hand subnucleus (see Kaas et al., '84). A more medial injection involving mostly the proximal forelimb labeled neurons more dorsally in the cell-dense portions of VP, where the proximal forelimb is represented in other primates. The most lateral injection was placed in cortex responsive to the upper lateral face, neck, and head. Labeled neurons were concentrated dorsally in cell-dense portions of medial VPl rather than VPm. This portion of VPl represents the shoulder, neck and possibly the back of the head (see Kaas et al., '84). Thus, the injection appeared to involve these body part representations in area 3b, and not the face region which is largely more rostrolateral in area 3b. In case 86-58 (Fig. 7), injections in parts of 3b representing the forearm labeled neurons in portions of dorsomedial VPl that have been shown to relate to forelimb in other monkeys. The injection in the shoulder representation labeled neurons in a more dorsal portion of VP than the injection in the forearm representation.

Connections of S-II

After injections centered in the forelimb portion of S-II (Figs. 7–10), anterograde and retrograde label was most dense in the portion of VPi just ventral to the hand subnucleus of VP (Fig. 8). Close inspection also revealed rows of labeled cells extending dorsally into VP, but com-

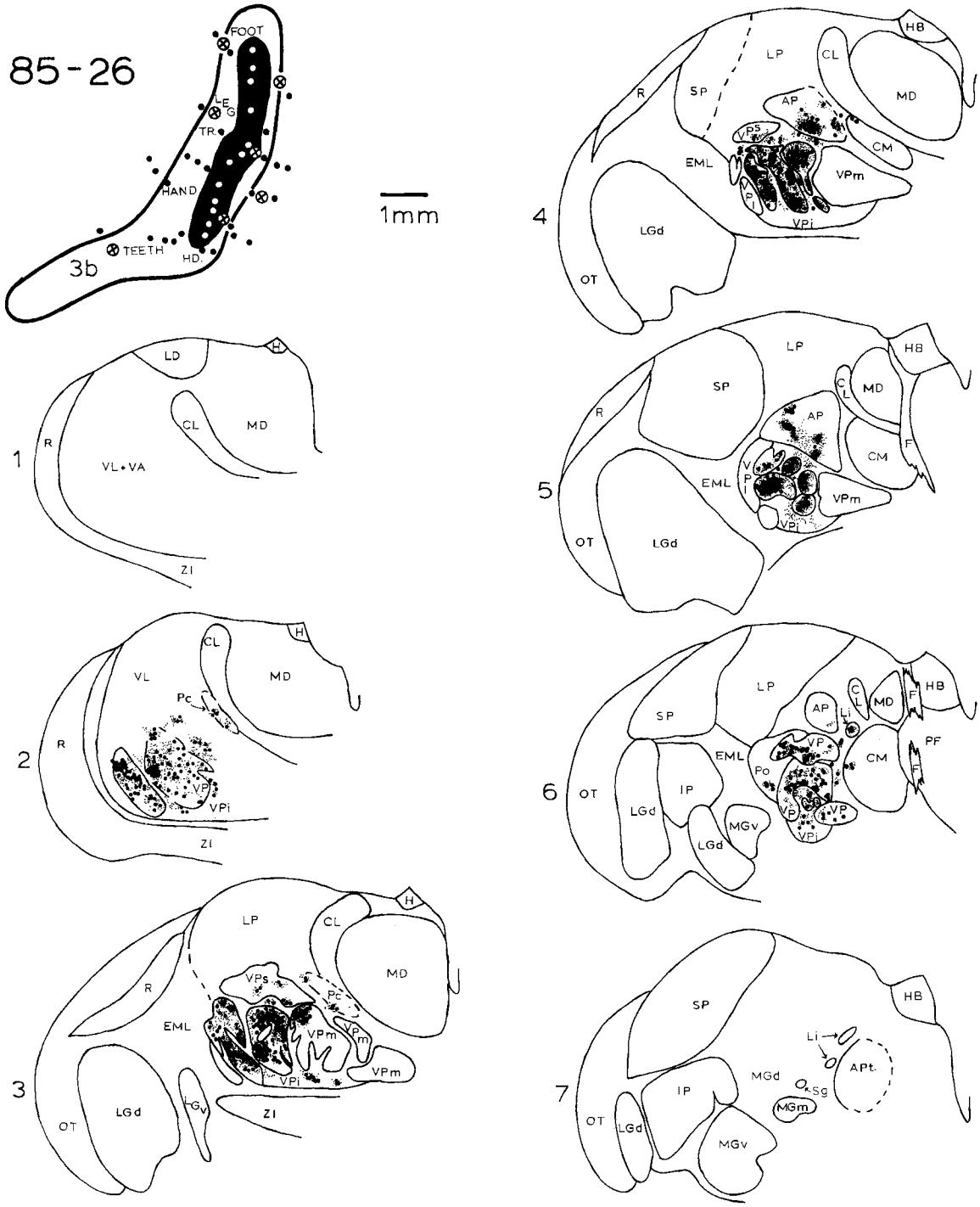


Fig. 5. The distribution of thalamic anterograde (small dots) and retrograde (large dots) label after a strip of WGA-HRP injections in area 3b. In the upper left figure the solid black region indicates the extent of the injections and white holes are micropipette punctures. See Krubitzer and Kaas ('90) for the location of area 3b in cortex, detailed mapping data for 3b of this case, cortical connections, and information on subsequent cases. The small dots represent electrode penetrations and the circles with Xs mark lesions placed at physiological boundaries. TR, trunk; HD, head. Thalamic sections 1–7 progress from rostral to caudal in 150 mm steps. Most label is in the ventral posterior nucleus. Other label is also in the anterior pulvinar, VPs, and Li. Large dots, labeled cell bodies; small dots, terminations. Thalamic and brainstem nuclei include anterior pretectum, APt., anterior pulvinar, AP; central lateral nucleus, CL; central medial nucleus, CM, external medullary lamina, EML; habenula, H or HB; fornix, F; inferior pulvinar, IP; lateral dorsal nucleus, LD; dorsal lateral geniculate nucleus, LGd; ventral lateral geniculate nucleus, LGv; limitans, Li; lateral posterior nucleus, LP; medial dorsal nucleus, MD; optic tract, OT; dorsal (MGd), medial (MGM) and ventral (MGv) divisions of the medial geniculate complex; paracentral nucleus, PC; parafascicular nucleus, PF; posterior nucleus, Po; reticular nucleus, R; suprageniculate nucleus, Sg; superior pulvinar, SP; ventral anterior nucleus, VA; ventral lateral nucleus, VL; ventroposterior nucleus, VP; ventroposterior inferior nucleus, VPi; ventroposterior superior nucleus, VPs; lateral subnucleus of VP, VPl; medial subnucleus of VP, VPm; zona incerta, ZI. Scale bar is for the thalamus.

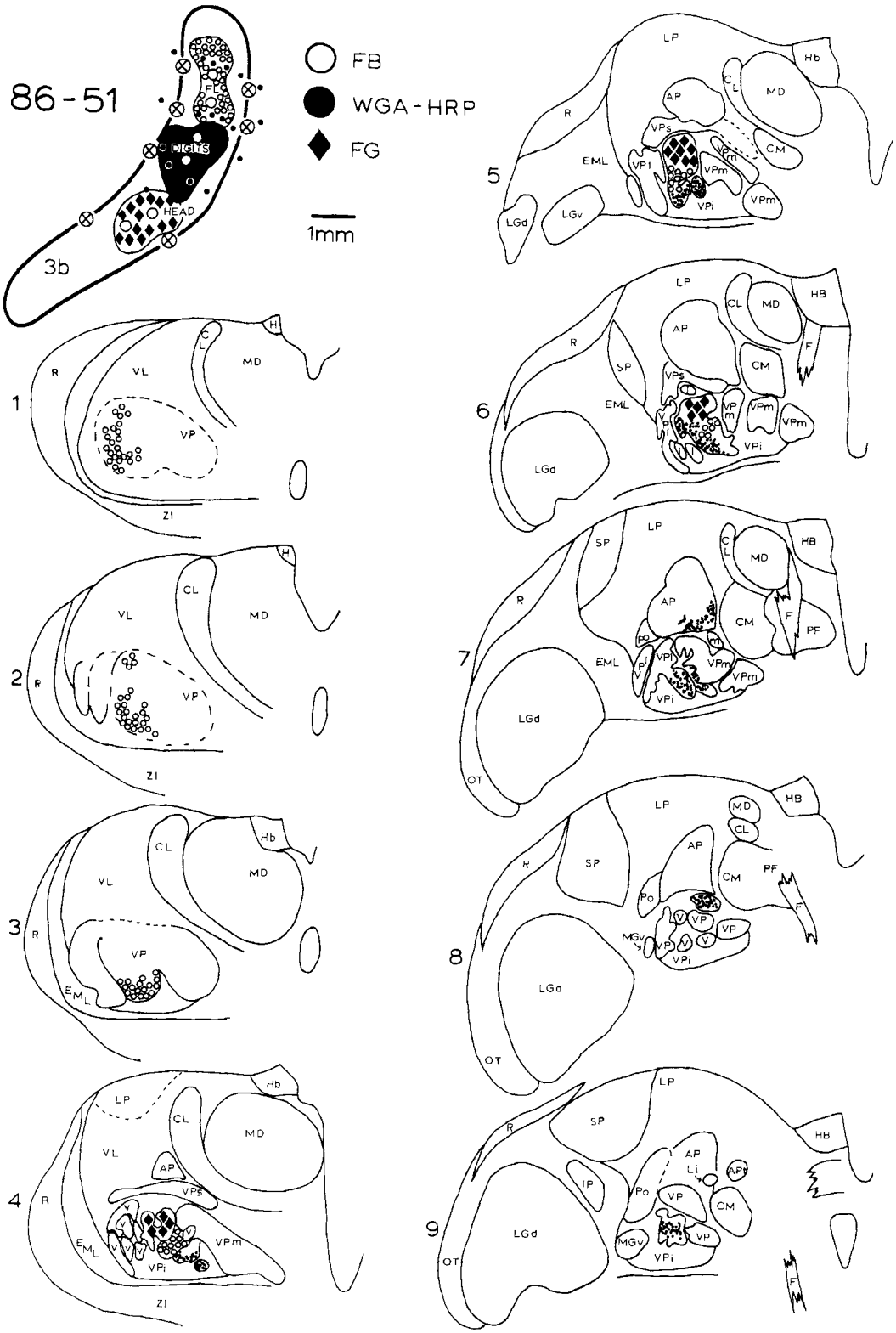


Fig. 6. Thalamic label after three separate tracers were injected into electrophysiologically identified body part representations in 3b. Injections into the digit representation labeled a ventral portion of VP; injections in the forelimb representation labeled more dorsal portions of VP; and injections in the head representation labeled far dorsal portions in VP. In this case, small amounts of label were also in the anterior pulvinar. Fast blue, FB; fluorogold, FG. m, medial subnucleus of VP. For the FB and FG injections, only labeled cell bodies were identified. For the WGA-HRP injection, symbols represent the distribution of anterograde and retrograde label. V = VP. Other conventions as in Figure 5.

pletely within the CO light regions that have smaller, pale-staining neurons. The continuity of these pale regions with VPi as well as similarities in architectonic appearance and connections with S-II constitute the principal evidence that VPi extends dorsalward to be partly embedded in VP. The segregation of neurons projecting to S-II within VPi proper and embedded VPi is evident throughout the rostrocaudal extent of the nucleus (Fig. 7). At all levels, neurons projecting to S-II were in the CO light portions of the VP regions rather than the CO dark, cell dense regions. The CO light regions were larger rostrally and caudally in the nucleus, and labeled neurons were found in these zones. In addition, labeled neurons and axon terminals were also noted in a narrow CO light region just dorsal to VP. Thus, we conclude that VPi is largely ventral to VP, but VPi also surrounds and is embedded in VP (Fig. 3). Furthermore, all parts of VPi project to S-II and receive projections from S-II.

The separation of neurons projecting to S-II from neurons projecting to S-I (3b) within the VP region was indicated most clearly in a case where the forearm representations of S-I and S-II were injected with different fluorescent tracers. In the same region of VP, neurons projecting to S-I were completely confined to the CO dark clusters of densely packed neurons while the neurons projecting to S-II were in adjacent tissue that was CO light and contained pale staining, smaller neurons (Fig. 7).

Some aspects of the somatotopic organization of VPi were revealed by placing injections in the representations of different body parts in S-II. In case 85-93, ^{3}H-WGA and WGA-HRP were placed in parts of S-II representing the hindlimb and glabrous digits of the hand, respectively (Fig. 10). Label resulting from the injection in the hindlimb representation was located more laterally in VPi and embedded VPi than label from the injection in the digit representation. Thus, the somatotopic organization of VPi appears to be at least roughly in parallel with that of VP.

Another observation is that after S-II injections significant numbers of labeled cells were located dorsal to VP in the anterior pulvinar, AP. In one case (86-58; Fig. 9), sparse label was also noted in Pc, CL, and MD.

Connections of PV

An injection of WGA-HRP centered in the representation of the head, neck and trunk in PV densely labeled cell bodies and axon terminals in VPi, especially in the more medial portion of the nucleus (Figs. 11, 12). The sparse label in the VPm region was largely around rather than in the dense cell clusters, and thus part of VPi. Label in this medial location, just ventral to VPm and in the parts of VPi embedded in VPm, suggests that the neck and upper trunk are represented medially in VPi. Moderate amounts of thalamic label were in AP. Sparse anterograde and retrograde label was observed more dorsally in LP. Finally, some label was in the magnocellular division of the medial geniculate complex, MGM, the medial dorsal nucleus, MD, and the ventral lateral nucleus, VL. Thus, label was more broadly distributed in the thalamus after the PV injection than after 3b or SII injections.

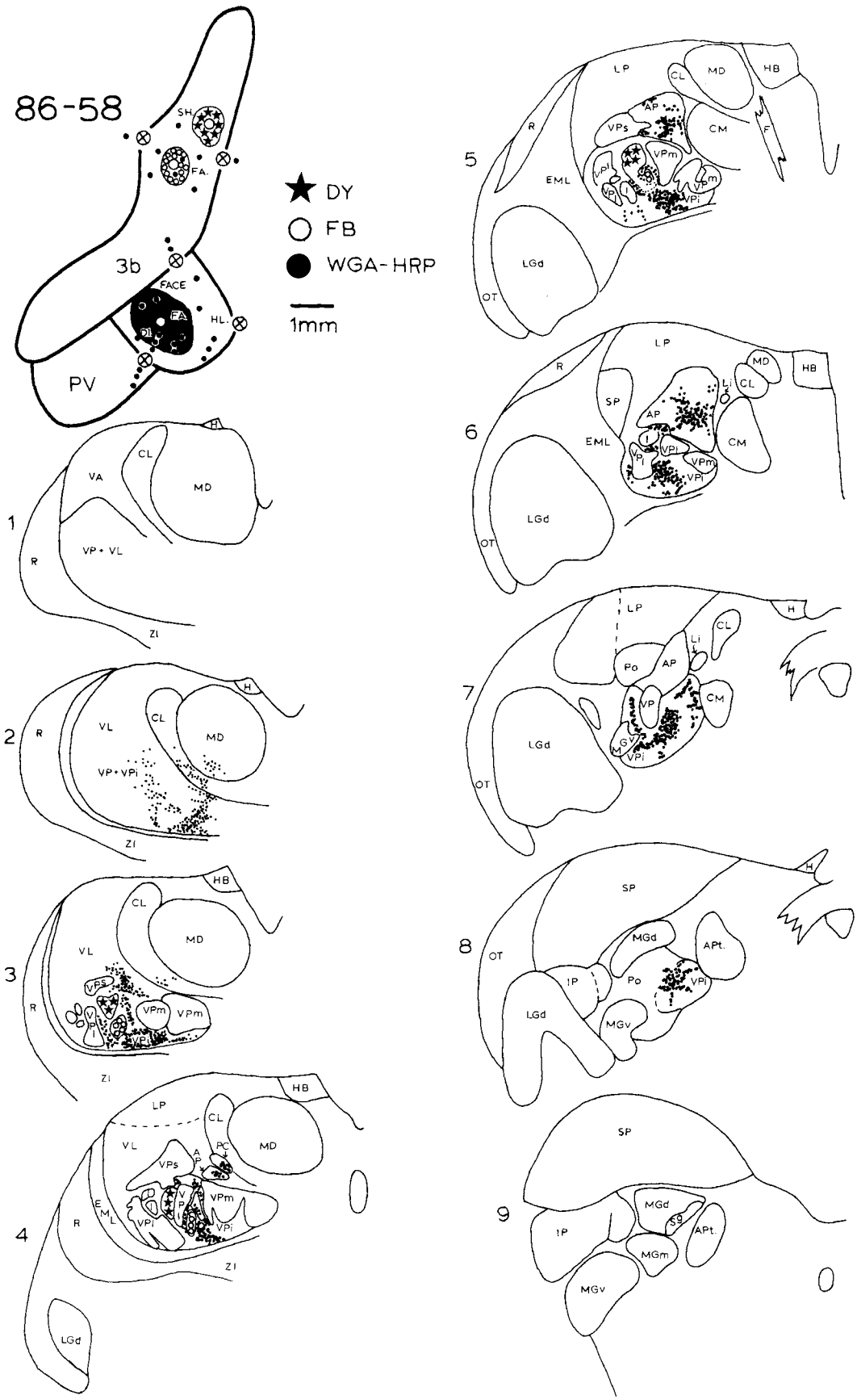
DISCUSSION

In the present study, we used injections of anatomical tracers to determine the thalamic connections of three different subdivisions of somatosensory cortex. Our most important conclusions are that the ventroposterior inferior nucleus, VPi, is the principal source of inputs to both S-II and the parietal ventral area, PV, and that VPi includes both a ventral portion as traditionally described, and dorsalward extensions that are embedded within and around VP. VP proper, which is densely packed with dark-staining larger neurons, projects to area 3b rather than the S-II or PV. These three cortical areas also receive inputs from the anterior pulvinar.

Connections of area 3b (S-I proper)

Present evidence supports the conclusions that the major source of thalamic input to area 3b of monkeys is from the ventroposterior nucleus (Fig. 13), and that neurons from all parts of this nucleus, when appropriately defined, are devoted to relaying information to area 3b. The first conclusion is hardly surprising. VP has long been known to project to area 3b (e.g., Clark and Powell, '53; Jones and Powell, '70; Jones, '75), and such connections have been established in more recent studies in a range of simian species including macaque monkeys (e.g., Nelson and Kaas, '81; Jones and Friedman, '82), owl monkeys (Lin et al., '79), Cebus monkeys (Mayner and Kaas, '86), squirrel monkeys (Cusick et al., '85; Cusick and Gould, '90; Ma and Juliano, '91), and now marmosets. We consider area 3b to be S-I proper, the homologue of S-I in prosimians and nonprimate mammals (see Kaas, '83). In all studied mammals, a major cortical target of VP appears to be S-I (see Krubitzer and Kaas, '87 for review). The second conclusion depends on distinguishing VP proper from the embedded portions of VPi. Present results indicate that only the clusters of densely packed, darkly stained, CO-dense portions of VP project densely to area 3b, and that the CO-light septa or matrix of pale staining, smaller, more sparsely distributed cells that separate the dense cell clusters contain neurons that rarely project to area 3b.

The concept that pale staining bands or septa parcellate VP into groups of cells related to different body parts is not new. VPl and VPm have long been distinguished as separate components of VP on the basis of a cell-poor separating lamina (see Jones, '85), and other such separating laminae segregating foot from hand, from tail representations, and even individual digits, have been noted for a number of mammals (see Welker, '73; Johnson, '80; Kaas et al., '84). Such cell-poor regions are especially evident as CO-light bands in sections reacted for cytochrome oxidase (Figs. 1, 2; also see Jones et al., '86a,b; Cusick and Gould, '90). Furthermore, in macaque monkeys, Jones et al. ('86a,b) have described the segregation of VPm into CO-dense clumps and CO-light septa, and have demonstrated that each of the CO dense clumps contains neurons that respond to light tactile stimuli on a given restricted body part. More recently, Rausell and Jones ('91b) demonstrated that the CO-dense aggregations contain the neurons that project to layer IV of area 3b, while small neurons in the septa or matrix project to layers I and II. Earlier, Penny et al. ('82) had reported that only the small cells in VP of cats were labeled after injections restricted to layers I and II of S-I. The present results indicate that the CO-dense regions of VP contain neurons that project to area 3b, while the CO-light regions contain neurons that largely project elsewhere. Injections of tracers in area 3b labeled neurons in the CO-dense rather than the CO-light regions, and when both area 3b and S-II were injected with different tracers, separate populations of neurons in the VP region were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SH
FA
3b
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FA
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PL
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1mm
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VA
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Figure 7

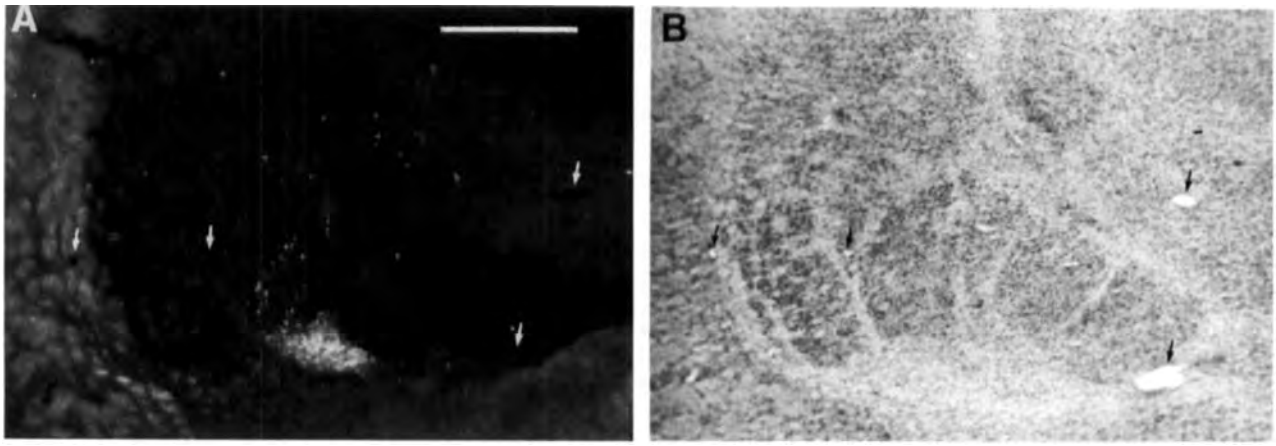

Fig. 8. Bidirectionally transported thalamic label after an injection of WGA-HRP in S-II. **A:** Darkfield photomicrograph of a thalamic section treated for HRP. **B:** Lightfield photomicrograph of adjacent section stained for Nissl substance. In this case, the forelimb representation in S-II was injected and transported tracer is found in the cell poor VPi nucleus. Sparse bands of label in embedded VPi also run through VP. Arrows mark blood vessels that match in the two sections. Medial, right. Scale bar, 1 mm.

labeled. Nevertheless, it remains possible that neurons in the CO-light regions also project to the superficial layers in area 3b, and our injections failed to label these neurons because they were centered in layer IV rather than layers I and II.

Other nuclei also project to area 3b, but much less densely. As Cusick and Gould ('90) described in squirrel monkeys, a few neurons in the anterior pulvinar (AP), VPs, and VPi are labeled after area 3b injections (Fig. 13). VPs is a dorsal capping nucleus of VP that has been commonly included in the dorsal part of VP in other reports (see Kaas et al., '84). The major connections of VPs are with areas 3a and 2 (VP shell of Friedman and Jones, '81; VPs of Pons and Kaas, '85; Cusick et al., '85, '89; Cusick and Gould, '90). A few labeled neurons were also found in the paracentral nucleus, pc, of the interlaminar group (Fig. 13). This result is consistent with the general conclusion that intralaminar nuclei project only sparsely to SI and SII (Macchi and Bentivoglio, '86).

Connections of S-II

The major projections to S-II originate from VPi proper and the portion of VPi embedded in VP (Fig. 13). Few, if any, neurons in VP proper appear to project to S-II. Previous interpretations of the sources of input to S-II in primates have varied. Early reports on S-II connections in monkeys described projections from VP rather than VPi (see Jones, '85), but more recently Friedman and Murray ('86) concluded that the major input to S-II was from VPi (also see Friedman et al., '83). In a more limited study directed towards understanding interhemispheric connections of somatosensory cortex, Manzioni et al. ('84) described VPi as densely labeled after S-II injections. In an earlier brief report, Loe et al. ('78) described both VP and VPi as sources of projections to S-II. Finally, in a study on the organization and connections of S-II in a prosimian primate, galago, Burton and Carlson ('86) concluded that both VP and VPi project to S-II.

The early view that VP provides the major thalamic input to S-II was largely based on evidence of projections to S-II that were revealed by lesions (Jones and Powell, '70) or injections (Burton and Jones, '76) in VP. Friedman and Murray ('86) suggest that the resulting label in SII could be from the lesions and injections involving VPi, in addition to VP, by interrupting fibers of passage or spread of the injection. Another possibility, suggested by present results, is that the terminations revealed in S-II were from neurons in the body of VP, but from neurons that we now relate to the portion of VPi that is embedded in VP, since present results locate neurons labeled by S-II injections in the CO light regions within VP that were judged to be extensions of VPi. Thus, the early results on VP projections in macaque monkeys are not necessarily incompatible with our proposal that distinctly different populations of neurons project to S-I (area 3b) and S-II in monkeys.

Most other mammals appear to differ from monkeys and perhaps primates in general in that VP proper does provide the major projection to S-II. Thalamic connections of S-II have been most intensively studied in domestic cats. In an early landmark study, Jones and Powell ('69) placed lesions in VP to reveal projections to S-I and S-II of cats (also see Macchi et al., '59). As for a later study on monkeys (Jones and Powell, '70), the lesions in VP could have interrupted projections from VPi or included portions of VPi embedded in VP. These possibilities are suggested not only by present results, but also by the finding of Herron ('83) that VPi rather than VP projects to S-II in raccoons. However, more recent experiments on cats seem to confirm earlier conclusions and demonstrate that VP provides the major thalamic projection to S-II (see Burton and Kopf, '84). Nevertheless, the bulk of the projection to S-II in cats appears to be in a

Fig. 7. Thalamic label after injections into electrophysiologically identified body part representations in 3b and S-II. The WGA-HRP injection in S-II and the fast blue injection in 3b were centered in the same body part representation. The S-II injection labeled proper and embedded portions of VPi while the injection in 3b labeled VP. The label in VPi was adjacent to the label in VP but was non-overlapping, suggesting a parallel organization in VPi and VP. Other label from the S-II injection was also in AP, CL, MD, Pc, and PV, the parietal ventral somatosensory area. For the DY and FB injections, symbols represent the distributions of retrograde label. For the WGA-HRP injection, symbols represent the distribution of anterograde and retrograde label. PC, paracentral nucleus. Other conventions as in Figure 5.

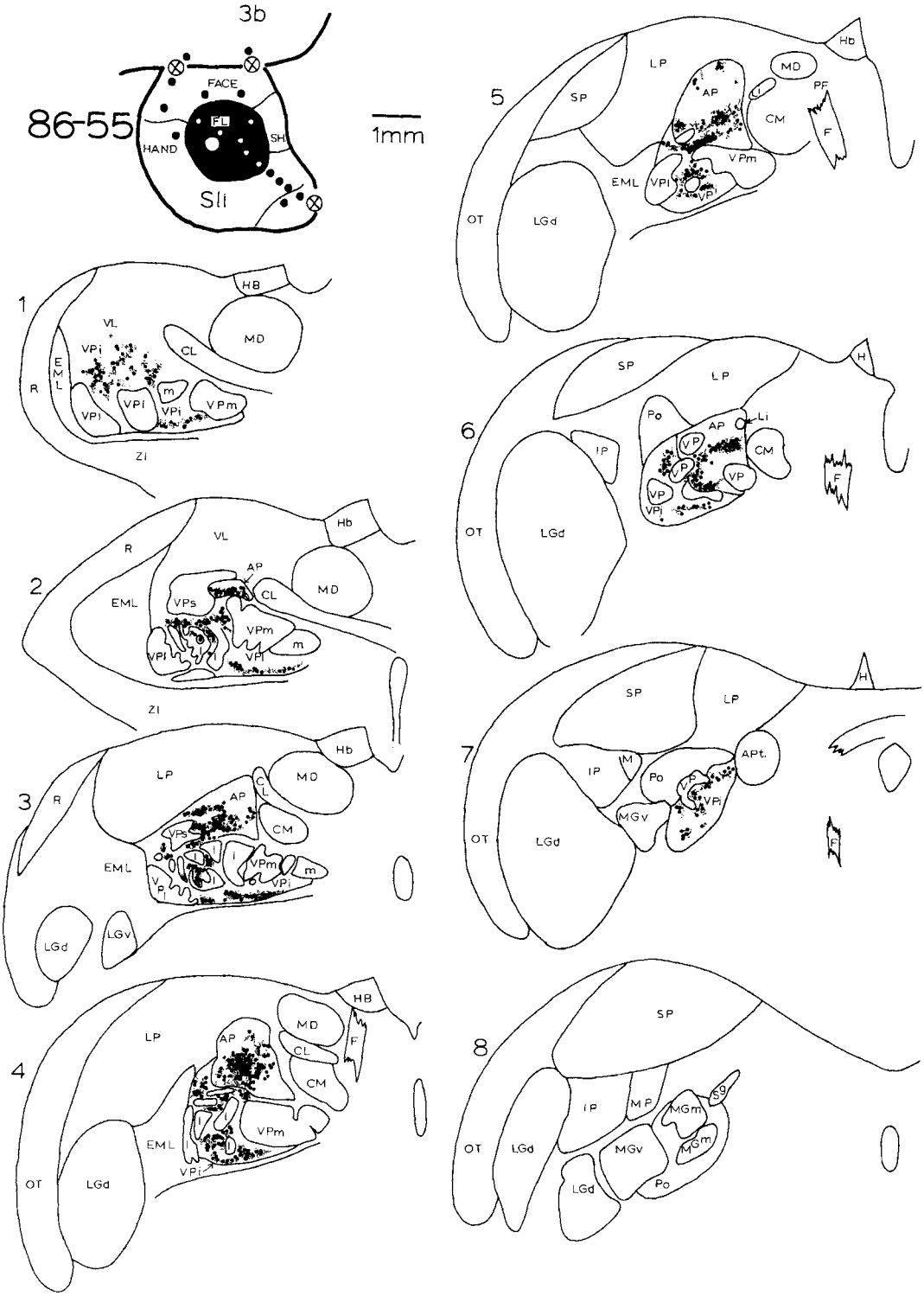

Fig. 9. Thalamic label after an injection of WGA-HRP centered in the forelimb (FL) representation in S-II. Label is found in VPi proper and VPi embedded. Dense label is also in the anterior pulvinar. SH, shoulder. M and MP, medial division of the inferior pulvinar. Other conventions as in Figure 5.

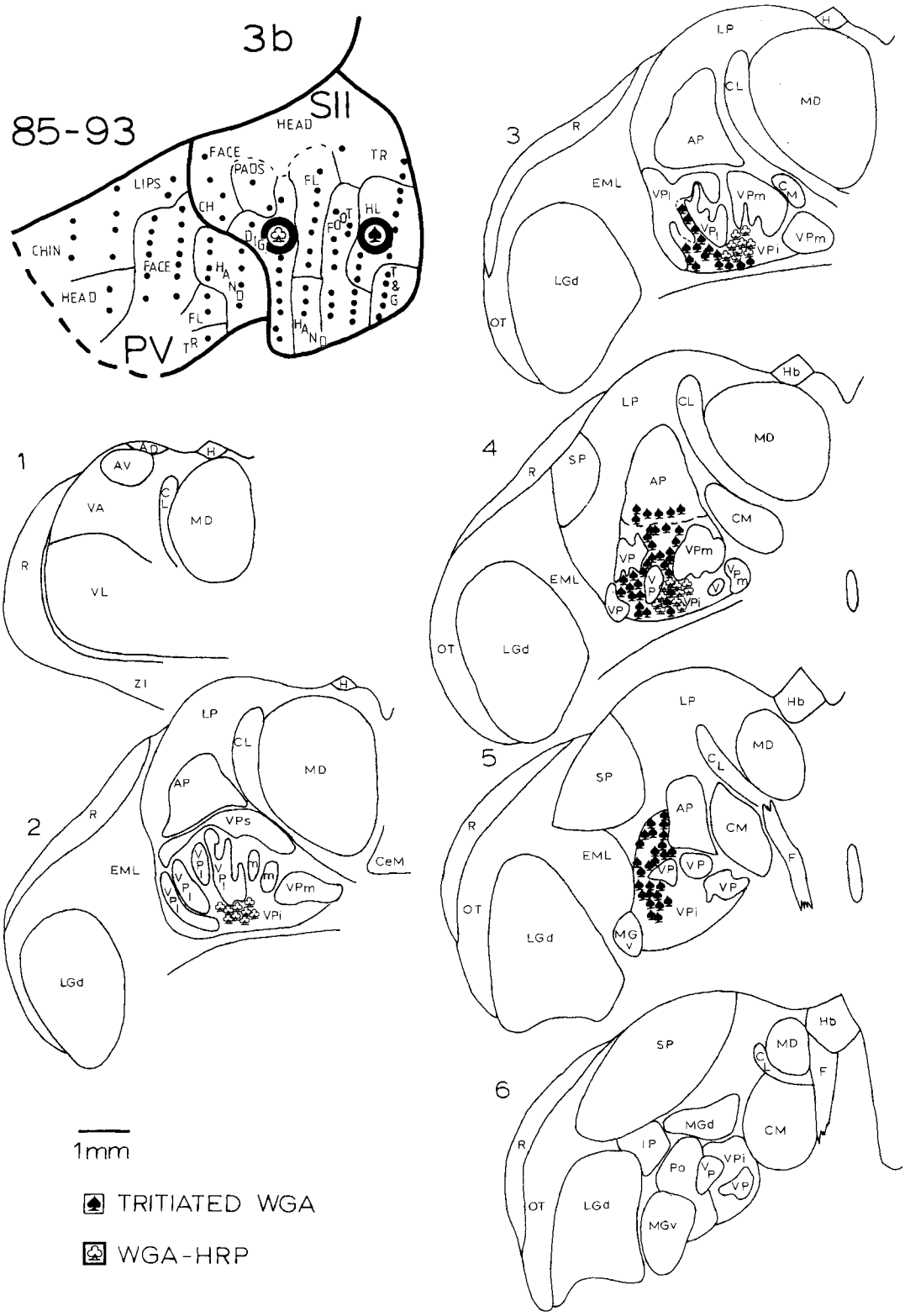

Fig. 10. Thalamic label after injections of two different tracers in two different electrophysiologically identified body part representations in S-II. Tritiated WGA was placed in the hindlimb representation in S-II and transported tracer is located laterally in VPi. Injections of WGA-HRP into the digit representation in S-II result in label in part of VPi that is medial to the label from the hindlimb injection, suggesting a topographic organization of VPi. For both the tritiated WGA and the WGA-HRP injections, symbols represent the distribution of both anterograde and retrograde label. In cortex: FL, forelimb; CH, chin; H, hand; HL, hindlimb; T & G, tail and gluteal region; TR, trunk. In the thalamus, anterior dorsal nucleus, AD; anterior ventral nucleus, AV; central medial nucleus, CeM. Other conventions as in Figure 5.

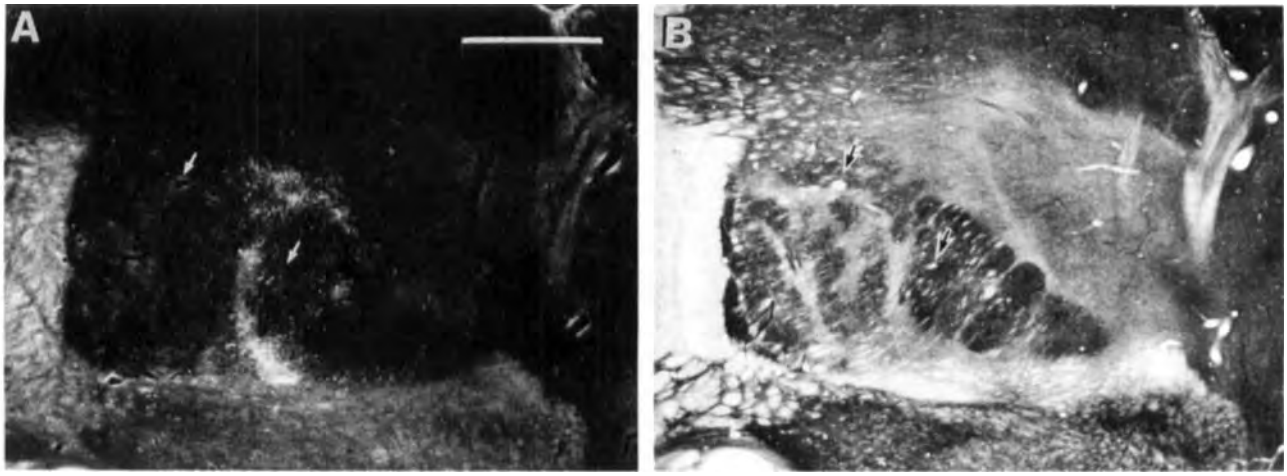

Fig. 11. Bidirectionally transported thalamic label after an injection of WGA-HRP into PV (see Fig. 12). Photomicrographs of adjacent thalamic sections reacted for HRP (A), or for CO (B). Note that the label is concentrated in ventral VPi and also extends into VPi embedded. A moderate amount of label also is in the lightly staining region just dorsal to VP that appears to be an extension of embedded VPi. Compare with Figure 8. Arrows mark matching blood vessels in the two sections. Scale bar, 1 mm.

surrounding "shell" or "fringe" of VP, rather than in the "core" projecting densely to S-I (see Spreafico et al., '81) and thus there seems to be a large degree of segregation of pathways from the thalamus to cortical areas S-I and S-II in cats as well as raccoons. While, the segregation is not complete, since some cells project to both S-I and S-II in cats (Speriafico et al., '81), doubly projecting neurons were only frequent in the fringe zone of VP and they were virtually absent in the "core" of VP with the dense input from the dorsal column nuclei. In rats (Bold and Neafsey, '84; Spreafico et al., '87) squirrels (Krubitzer and Kaas, '87) and tree shrews (Weller et al., '87), neurons in VP provide a substantial projection to S-II. Thus, it appears that the pathways to S-I and S-II are highly segregated in monkeys and raccoons, while being only partially segregated in cats and even less so in rodents and tree shrews. Prosimian primates may resemble tree shrews and other mammals in that Burton and Carlson ('86) report that injections in S-II of galagos label many neurons in VP. Megachiropteran bats resemble monkeys and raccoons in that projections to S-I originate largely in VP while those to S-II and PV are from a segregated VPi (Krubitzer and Calford, '92).

Interestingly, lesions of S-I abolish the responsiveness of S-II to cutaneous stimuli in monkeys (Pons et al., '87; Garraghty et al., '90a), but not in cats (Manzoni et al., '79), tree shrews, or galagos (Garraghty et al., '91). One interpretation of this difference in the consequences of S-I lesions is that a certain level of direct VP projections is needed to maintain S-II responsiveness, and that this level is lacking in monkeys, but present in cats, galagos, and tree shrews.

The present experiments also provided evidence for a systematic representation of the body in VPi. Injections in the forelimb region labeled the part of VPi just ventral to the forelimb representation in VP, and injections in two different locations in S-II labeled two separate, but partly overlapping, regions in VPi. The results were consistent with the proposal of Herron ('83), based on label in VPi after injections in different parts of S-II in raccoons, that VPi systematically represents the body surface.

Other labeled neurons were found in the anterior pulvinar after S-II injections. Similar connections have been described after S-II injections in macaque monkeys (Friedman and Murray, '86). In prosimian galagos, S-II injections labeled neurons in the location of the anterior pulvinar, but the labeled region was included in the posterior complex (PO) by Burton and Carlson ('86). In cats (Spreafico et al., '81) and rodents (see Krubitzer and Kaas, '87), S-II injections label neurons in the medial posterior nucleus, Pom.

Connections of PV

The parietal ventral area, PV, is a recently described somatosensory area, first reported for squirrels (Krubitzer et al., '86; Krubitzer and Kaas, '87) and subsequently in marmosets (Krubitzer and Kaas, '90). In addition, there is evidence for PV in rats (Li et al., '90; Fabri et al., '90) and in a megachiropteran, the flying fox (Krubitzer and Calford, '92). Since PV appears to exist in such distantly related mammals as rodents and primates, PV may be a somatosensory area basic to most or all mammals.

In marmosets, PV has major inputs from VPi, while other inputs come from the anterior pulvinar, AP, the lateral posterior nucleus, LP, and sparsely from the magnocellular division of the medial geniculate nucleus (Fig. 13). While the thalamic connections of PV have not been directly studied in any other primate, cortex in the region of PV has been shown to have connections with VPi and AP in macaque monkeys (Burton and Jones, '76; Friedman and Murray, '86). In squirrels, PV receives input from VP, VPi, and the magnocellular division of the medial geniculate complex (Krubitzer and Kaas, '87).

The ventroposterior inferior nucleus

VPi appears to have two parts; one portion ventral to VP and one part extending up in a finger-like manner to subdivide and partially surround VP (Fig. 3). More rostral and especially caudal parts of VP are engulfed by more of VPi. Both parts of VPi relay information to S-II and PV.

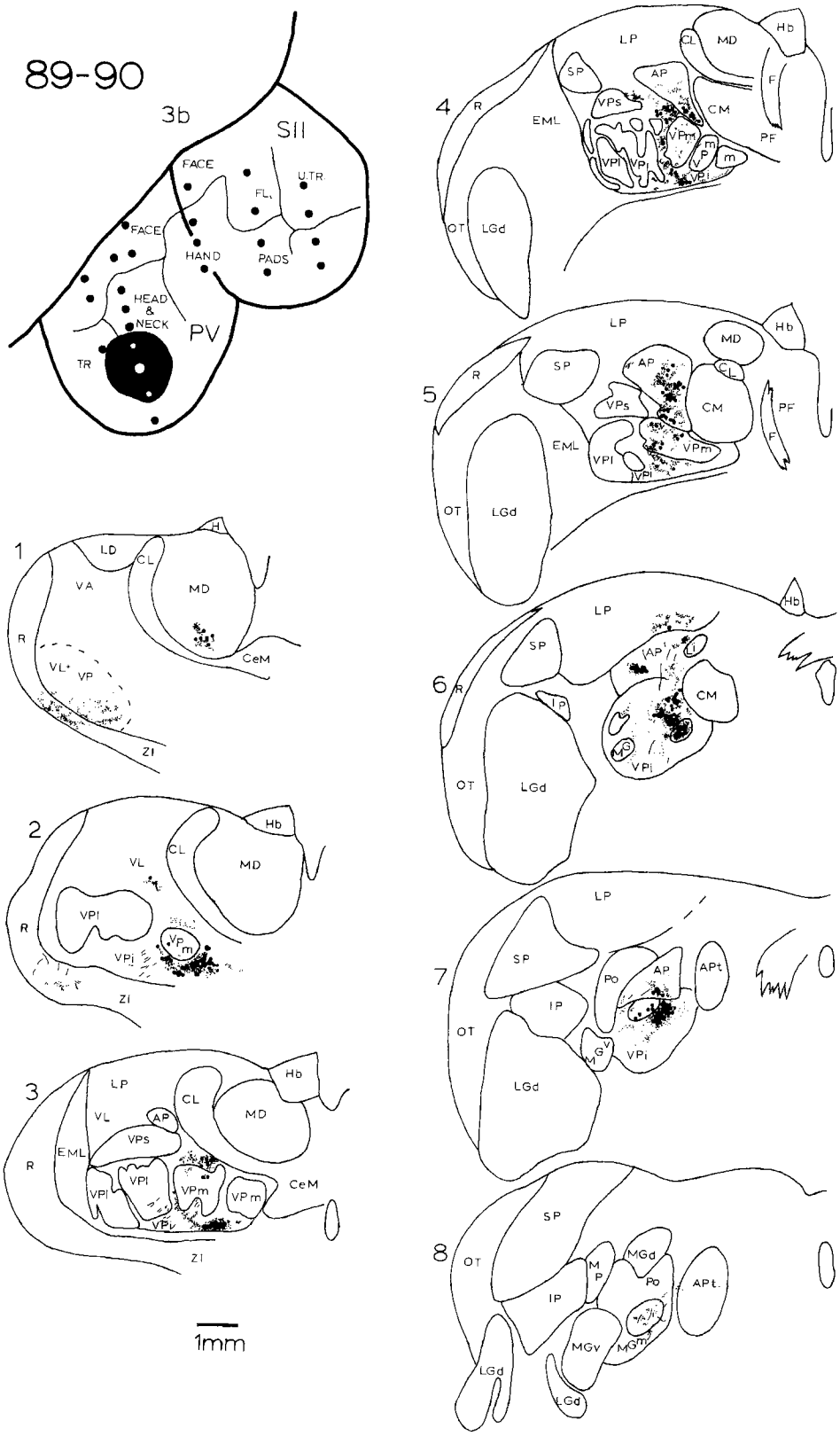

Fig. 12. Thalamic label following an injection of WGA-HRP centered in the upper trunk/head and neck representation in PV. Dense label is in the far ventral portion and in the rostral and caudal poles of VPi. Label is also apparent in AP, VL, Li, LP, and MGm. U.Tr, TR, trunk. Other conventions as in previous figures.

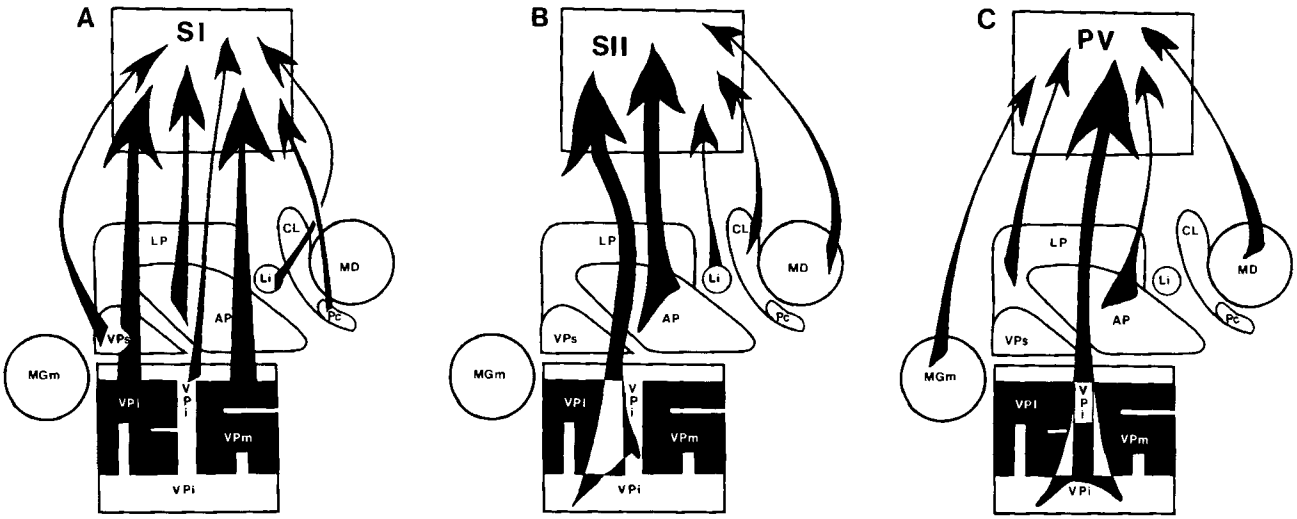

Fig. 13. A summary of the connections of 3b, SII and PV with the somatosensory thalamus. The densest connections of SI are with VP, while moderate to sparse inputs originate in AP, VPs, VPi, Li, and Pc. S-II has dense inputs from both embedded and ventral parts of VPi and from AP. The major inputs to PV are also from VPi. See Figure 5 for abbreviations.

The major source of sensory information to both parts of VPi appears to be the spinothalamic tract (e.g., Boivie, '79; Berkley, '80; Mantyh, '83; Apkarian and Hodge, '89; Gingold et al., '91; also see Rausell and Jones, '91b). There have been suggestions that VPi neurons are activated by pacinian afferents (Dykes et al., '81), but this seems unlikely since such information would depend on dorsal-column rather than spinothalamic pathways (see Kaas and Pons, '88, for review). Another proposal was that VPi relays vestibular information (Deecke et al., '74), but projections from the vestibular nuclear complex to VPi appear to be, at best, sparse (Lang et al., '79). Instead, the dense inputs from spinothalamic neurons most likely provide information about tactile stimuli that extend into the painful range of intensities (Ferrington et al., '87; Kenshalo et al., '79; Gingold et al., '91), a possibility that is supported by limited evidence from recordings from VPi (Casey and Morrow, '87).

Remarkably, the relay of information from VPi to S-II and PV does not directly activate neurons in these fields. Instead, both S-II and PV depend on S-I proper and adjoining cortex (area 3b and perhaps area 1) for activity related to cutaneous receptors and probably 3a and area 2 for activity related to deep receptors (see Pons et al., '87; Garraghty et al., '90a,b). Thus, the VPi inputs must have a modulating role on the activity of neurons that are normally responsive to non-painful levels of somatosensory stimuli, possibly by enhancing activity. S-II and PV are stations in a processing hierarchy directed from anterior parietal cortex toward the amygdala and hippocampus. This system is thought to mediate tactile learning and memory (Mishkin, '79; Friedman et al., '86). Intense stimuli that extend into the painful range may increase the overall activity in S-II and PV and thereby provide information about noxious aspects of stimuli that are identified and remembered (also, see Kaas and Garraghty, '91).

Our proposal that VPi has both ventral and embedded components may account for the fact that VPi does not seem to be well defined in most mammals (see Jones, '85). In most mammals, VPi may form a thinner shell around VP and be more restricted to ventral and caudal ends of VP and to regions parcellating the body representation in VP than forming a distinctive ventral nucleus as in primates and raccoons. In this regard, VPi resembles the dysgranular zones embedded in granular S-I of rats and mice (e.g., Chapin and Lin, '84), which may be homologous to the more segregated area 3a of primates and cats (see Li et al., '90 for review) or the embedded 1-2 region in 3b of megachiropterian bats (Krubitzer and Calford, '92).

The anterior pulvinar

The anterior pulvinar is a subdivision of the thalamus of monkeys and other larger primates that doesn't exist in descriptions of thalamic organization of non-primates or even prosimian primates. Instead, the comparable region is included in the posterior complex, often in the posterior medial nucleus, Pom. It is gradually becoming apparent that the anterior pulvinar connects with a range of somatosensory areas including posterior parietal cortex (e.g., Burton and Jones, '76; Jones et al., '79; Schmahmann and Pandya, '90), areas 1, 2, and 3b of anterior parietal cortex (Pons and Kaas, '85; Cusick and Gould, '90), and S-II and PV (present report). These connections are very much like the connections of Pom in a number of mammals, which include S-I and S-II (see Krubitzer and Kaas, '87). Thus, present results on anterior pulvinar connections in marmosets reinforce previous suggestions that the anterior pulvinar of primates corresponds to POM of other mammals (Jones, '85; Krubitzer and Kaas, '87).

ACKNOWLEDGMENTS

The research was supported by NIH grant NS 16446.

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