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Thalamocortical connections of the parietal ventral area (PV) and the second somatosensory area (S2) in macaque monkeys

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Abstract

Neuroanatomical tracers were injected into two functionally distinct areas in the lateral sulcus of macaque monkeys, the parietal ventral area (PV) and the second somatosensory area (S2). Three of the four injection sites were electrophysiologically determined by defining the receptive fields of neurons at the injection site prior to the placement of the anatomical tracers. Additionally, all locations were confirmed myeloarchitectonically. Labeled cell bodies and axon terminals were identified in the ipsilateral dorsal thalamus and related to nuclear boundaries in tissue stained for cytochrome oxidase (CO) and Nissl substance. Our results indicate that PV receives substantial input from the inferior division of the ventral posterior nucleus (VPi), the anterior pulvinar (Pla), and from the ventral portion of the magnocellular division of the mediodorsal nucleus (MDm), which also is interconnected with prefrontal cortex, the entorhinal cortex and the amygdala. S2 receives input predominantly from VPi, the ventral posterior superior nucleus (VPs), and Pla. These results indicate that PV and S2 are involved in processing inputs from deep receptors in the muscles and joints. Because PV and S2 receive little if any cutaneous input from the thalamus, cutaneous input to these fields must arise mainly through cortical connections. Connectional data supports the proposition that PV and S2 integrate motor and somatic information necessary for proprioception, goal directed reaching and grasping and tactile object identification. Further, PV may play a role in tactile learning and memory. © 2002 Published by Elsevier Science Ltd.

Keywords: Somatosensory neocortex; Sylvian fissure; Electrophysiology; Sensorimotor integration

1. Introduction

In primates, the somatosensory system plays an important role in complex behaviors such as manual dexterity, bilateral coordination of the hands, and goal directed reaching. Since the early work of Woolsey and Fairman, 1946; Woolsey, 1958; Penfield and Rasmussen, 1968, significant advances have been made in understanding the organization of cortex that subserves these functions. Specifically, somatosensory cortex of the lateral sulcus has been re-examined to reveal multiple cortical areas in addition to the second somatosensory area (S2). An additional cortical field, the parietal ventral area (PV) has been physiologically identified rostral to S2 in a variety of mammals (e.g. Krubitzer et al., 1986; Krubitzer and Calford, 1992; Beck et al., 1996; Huffman et al., 1999) including marmoset monkeys (Krubitzer and Kaas, 1990), macaque monkeys (Krubitzer et al., 1995a) and humans (Disbrow et al., 2000).

Although the majority of previous work examining this region was done prior to the identification of PV, it is clear that neurons in S2 and surrounding fields are less modality specific than neurons in S1, and have larger, often bilateral, receptive fields (e.g. Sinclair and Burton, 1993; Whitsel et al., 1969; Disbrow et al., 2000; Hinkley et al., 2001). Further, work in humans (Huttunen et al., 1996; Disbrow et al., 2001; Forss and Jousmäki, 1998; Hinkley et al., 2001; Lin et al., 2000) and non-human primates (Whitsel et al., 1969; Robinson and Burton, 1980a,b) indicates that some areas in the lateral sulcus, including S2, may be involved in integrating inputs within and across the hands and in sensorimotor integration. Studies in awake monkeys demonstrate that some neurons in S2 respond during active touch (Sinclair and Burton, 1993), and that neural activity in the S2 region in human and non-human primates is

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Nomenclature

Cortical areas and thalamic nuclei

1	somatosensory area 1
2	somatosensory area 2
3a	somatosensory area 3a
3b	primary somatosensory area
7b	somatosensory area in the lateral sulcus and inferior parietal lobule
A1	primary auditory area
CeM	central medial nucleus
CL	central lateral nucleus
CM	center médian nucleus
EML	external medullary lamina
F	fasciculus
HB	habenular nuclei
IML	internal medullary lamina
LD	lateral dorsal nucleus
LGd	dorsal division of the medial geniculate nucleus
LP	lateral posterior nucleus
MD	mediodorsal nucleus
MDm	magnocellular division of the mediodorsal nucleus
MDp	parvocellular division of the mediodorsal nucleus
Pc	paracentral nucleus
PF	parafascicular nucleus
Pa	anterior pulvinar nucleus
Pll	lateral pulvinar nucleus
PV	pariatel ventral area
S2	second somatosensory area
VL	ventral lateral nucleus
VMB	basal ventral medial nucleus
VP	ventral posterior nucleus
VPi	inferior division of the ventral posterior nucleus
VPl	lateral division of the ventral posterior nucleus
VPm	medial division of the ventral posterior nucleus
VPs	superior division of the ventral posterior nucleus
VS	ventral somatosensory area

Body parts and anatomical directions

fl	forelimb
D	dorsal
hl	hindlimb
M	medial
sh	shoulder
R	rostral
tr	trunk
utr	upper trunk

modulated by shifts in attention (Hsiao et al., 1993; Burton et al., 1997, 1999; Steinmetz et al., 2000).

While we and others have examined some aspects of complex somato-motor behaviors in humans using functional imaging techniques, these results are necessarily limited to examining indirectly the spatial organization and temporal processing of cortical fields involved in these behaviors. Presently, there are no techniques that allow connections of cortical areas to be described in human primates. Thus, non-human primates serve as an excellent model, because connections of homologous cortical areas and subcortical nuclei can be directly studied and the results can be extrapolated to humans. In the non-human primate we can appreciate the precise nature of somatosensory inputs to a particular neural structure, as well as inputs from other sensory systems, and we can also determine the sensory and motor structures to which the area in question projects.

We hypothesize that patterns of connections of S2 and PV reflect the observations that these fields are involved in complex behaviors such as integration of inputs across the hand, proprioception, and sensorimotor integration. In this case, one would expect to see interconnections between topographically matched and mismatched locations of the hand representation within and across cortical fields and thalamic nuclei. Further, one would also predict that these regions ultimately receive input from deep receptors in the muscles and joints. Finally, it is likely that S2 and PV have interconnections with motor regions of the cortex and associated thalamic nuclei. Our goal was to determine if any of these predictions are true by examining the thalamocortical connections of functionally identified locations in S2 and PV. The present investigation is part of a larger effort to determine the pattern of connections of S2, PV and surrounding cortical areas, as well as to examine the role these fields play in such complex behaviors as tactile object identification and goal directed reaching.

2. Methods and techniques

2.1. Surgical preparation, tracer injections and electrophysiological recording

The thalamocortical connections of PV and S2 were examined in three macaque monkeys (*Macaca mulatta*) by injecting neuroanatomical tracers into electrophysiologically identified locations. All surgical techniques were performed under standard sterile conditions. Monkeys were initially anesthetized with ketamine hydrochloride (10 mg/kg). The animals were then intubated, cannulated, and anesthesia was maintained using the inhaled anesthetic Isoflurane (1.5–2%). Throughout the entire experiment, body temperature, heart rate, respiration rate, and Pa O_2 levels were monitored. Once anesthetized, the skin was cut, the temporal muscle was retracted, and an opening was made in the skull over the lateral sulcus. The dura was then cut and retracted. In one case, the fluorescent tracer fluororuby was injected through

a Hamilton syringe (0.25–0.4 μl of 7%). After the injection was complete, a soft sterile contact lens was placed over the opening, the dura flaps were placed over the contact lens, the skull was replaced and cemented with dental acrylic, and the muscle and skin were sutured. For this case, the animal was allowed to recover for 2 weeks subsequent to electrophysiological recordings. Three WGA-HRP injections were placed at electrophysiologically identified locations at the beginning of the acute phase of experiments. The transport time for these cases was 24 h.

For recording experiments, the anesthetic, surgery, and monitoring regime was like that described above, except a urinary catheter and arterial line were placed at the beginning of the experiment, and the animal was artificially ventilated. Once this preparation was complete, the opening in the skull was enlarged and an acrylic well was built around the opening and filled with dimethylpolysiloxane. An image was taken of the exposed cortex with a Pixera PVC100C digital camera (Pixera Corp., Los Gatos, CA, USA), and printed, so that electrode tracks could be related to vascular patterns.

An electrode designed to record from multiunit clusters (5 MΩ, 0.02 in. diameter), was lowered into the cortex using a Kopf 650 hydraulic stepping microdrive (David Kopf Instruments, Tujunga, CA, USA). Recordings were made at various depths within the lateral sulcus, and at 700–1000 μm from the pial surface for recordings oriented perpendicular to the cortical surface. Neural recordings of multiple unit clusters were amplified, filtered (250 Hz to 4 kHz), viewed on an oscilloscope and heard through an audio monitor. Stimuli consisted of light taps, displacement of hairs with brushes, light brushing of skin, hard taps, and manipulation of muscles and joints. Receptive fields were drawn onto pictures of the body. Descriptions of the receptive fields and the type of stimulus required to elicit a response were also documented.

The electrode was advanced nearly perpendicular to the lateral sulcus and receptive fields were defined in 500 μm steps. Electrolytic lesions (10 μA for 10 s) were placed at strategic locations, and large probes made of pasta were inserted around the mapped area to aid with electrode penetration angle identification and serial reconstruction. At the conclusion of electrophysiological recordings, the animal was euthanized (60 mg/kg pentobarbital sodium) and transcardially perfused with 0.9% saline followed by 3% paraformaldehyde in phosphate buffer (pH = 7.3), and then 3% paraformaldehyde in 10% sucrose phosphate buffer. All protocols used in these experiments were approved by the Animal Use and Care Administrative Advisory Committee of the University of California, Davis, and conformed to NIH guidelines.

2.2. Tissue preparation and histological processing

At the end of the perfusion, the brain was removed from the cranium, and the brainstem and thalamus were separated from the cortex and left to soak overnight in 30% sucrose phosphate buffer. Three cortices were sectioned tangentially, at a thickness of 40–60 μm, and one cortex was sectioned horizontally at a thickness of 80 μm, and alternate sections were stained for myelin (Gallyas, 1979), reacted for HRP using tetramethylbenzidine (Mesulam, 1978; modified by Gibson et al., 1984), or mounted for fluorescent microscopy. The thalamus was cut in the coronal plane at a thickness of 60–65 μm. Alternate series of sections through the thalamus were stained for Nissl, reacted for cytochrome oxidase (CO) (Carroll and Wong-Riley, 1984), mounted for fluorescent microscopy, or reacted for HRP using tetramethylbenzidine (as mentioned above).

2.3. Data analysis

To match the cortical reconstructions to electrophysiological recording data, the brains were drawn to the same scale as the digital image marked with electrode penetrations. The electrode penetrations were matched in both data sets by utilizing the pasta probes, entry sites, and tissue damage. The recording depths were determined from electrolytic lesions, and the receptive field and stimulus preference for neurons at different depths were transposed onto the reconstructions. Thus, it was possible to reconstruct the injection site and its relation to architectonic boundaries and electrophysiological recordings.

Labeled cell bodies in the thalamus resulting from the injection of fluororuby were plotted relative to tissue artifacts, blood vessels, lesions, portions of electrode tracks, and the outline of sections using a Zeiss axioscope, with an X/Y stage encoder attached to a digitizer and computer. Labeled cell bodies and axon terminals for the WGA-HRP injections were plotted using a camera lucida attached to a Zeiss SV6 stereomicroscope. As with the fluorescent sections, the landmarks listed above were related to plotted cell bodies and axon terminals. For the reconstructions of the injections in cortex, all sections included an outline of the injection site and the zone of uptake. Details for determining the effective uptake zone have been described previously (Krubitzer et al., 1998). This reconstruction was then matched to tissue stained for myelin by aligning blood vessels and other tissue landmarks, and the architectonic boundaries of cortical fields were drawn onto the reconstruction for each case. For all cases, the entire series of myelin stains were used to determine these boundaries. For the thalamus, labeled cell bodies and axon terminals were matched to adjacent sections stained for Nissl or CO in the manner described for the cortex. Reconstruction was done for the entire series of sections in which labeled cells and terminals were identified.

3. Results

3.1. Electrophysiological recordings and the relation of injection sites to cortical maps

Three of the four injections were electrophysiologically defined so that the body part representation injected in either

PV or S2 could be determined. The location of the injection sites and electrophysiological recordings were related to cortical myeloarchitecture so that the position of the injection in relation to the boundaries of either PV or S2 could be appreciated. As described previously (e.g. Robinson and Burton, 1980a,b; Krubitzer et al., 1995a), the lateral sulcus is divided into a number of discrete cortical fields. The topographic organization of two of these fields, PV and S2 has been well characterized (e.g. Krubitzer et al., 1995a; Disbrow et al., 2000) and, therefore, descriptions of the fields provided here are brief (Fig. 1). Electrophysiological recordings in the present investigation confirmed previous findings indicating that neurons in PV and S2 have large, cutaneous receptive fields that are sometimes bilateral. Further, when architectonic boundaries were related to electrophysiological recordings, PV and S2 were found to be co-extensive with a moderately myelinated region adjacent to the ventral boundary of areas 3b and 1 (Fig. 1).

In PV, receptive fields for neurons at the center of the injection site for case 99-6 LM (Fig. 2A) were on the hand and face, and spread into the expected location of the oral structures (Fig. 1; as shown in Krubitzer et al., 1995a). The receptive fields for neurons at the center of the injection site for the other PV injection were bilateral on the ventral upper trunk and proximal forelimb (Fig. 2 B). Only one of the two S2 injections was electrophysiologically identified. For case 98-26 LM, the injection site was centered in an area containing neurons with receptive fields on the forelimb and hand (Fig. 2 C), but likely spread on to the face as well. Although the injection site for case 99-6 was not defined electrophysiologically, architectonic analysis demonstrated that as with the other injections, the injection site was well within the boundaries of the field (Fig. 2 D). Further, based on previous maps, the injection was in the expected location of the forelimb/face representation in S2.

3.2. Architecture of the dorsal thalamus and delineation of nuclear boundaries

In the following results, we use most of the terminology of the thalamic nuclei proposed by Jones (1985, 1998) who has extensively compared the thalamic boundaries in different species, and the nomenclature used by different investigators. The boundaries of thalamic nuclei were determined using Nissl stained sections and sections reacted for CO, which were highly effective for identifying the boundaries of major thalamic nuclei. Several nuclei of the somatosensory thalamus are readily defined because of the high contrast in the intensity of staining and density of neurons with adjacent nuclei. For instance, at middle levels of the

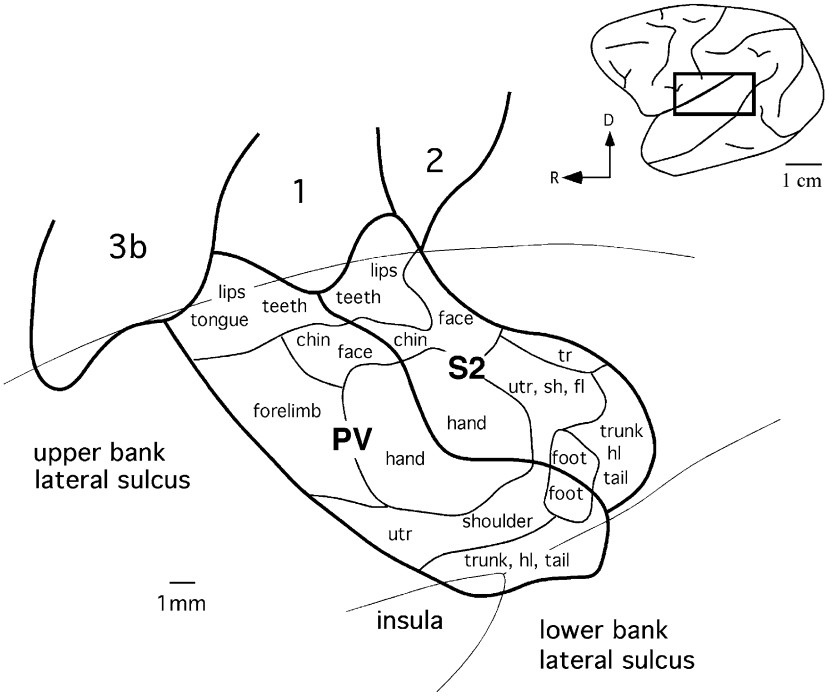

Fig. 1. The top right figure is a lateral view of the macaque monkey brain with the region of the lateral sulcus that contains S2 and PV enclosed in the box. The bottom figure is a summary of the topographic organization of cortical fields PV and S2 obtained from extensive electrophysiological exploration of these fields in previous investigations (modified from Krubitzer et al., 1995a). These maps were obtained by recording neurons from a number of closely placed sites where the type of stimuli that excited the neurons at this location, and receptive field of the neurons were recorded. Architectonic boundaries were then superimposed to make a comprehensive reconstructions of these fields. S2 and PV form mirror symmetric representations that are joined at the representations of the face, hands and feet. Proximal body part representations are at the rostral and caudal portions of PV and S2, respectively. Rostral is to the left and medial is to the top. (As shown in nomenclature for abbreviations).

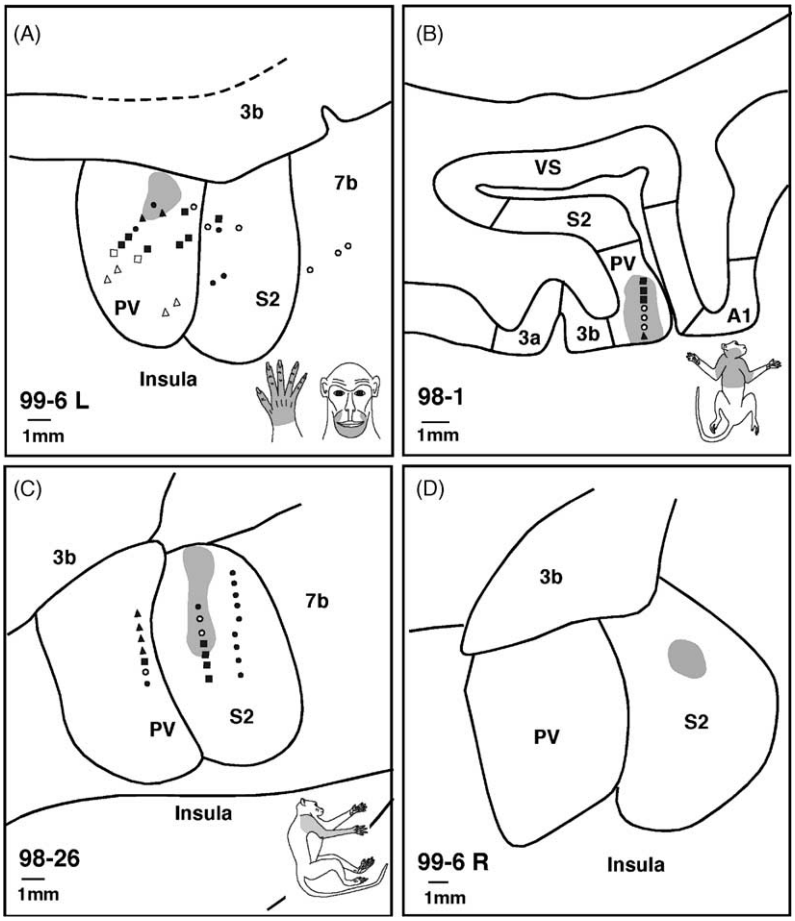

Fig. 2. Reconstructions of the injection sites in PV (A and B) and S2 (C and D), and their relation to architectonic boundaries and electrophysiological recordings. Architectonic boundaries (solid lines) were obtained by examining the entire series of sections through the cortex that were stained for myelin using the Gallyas (1979) method. Histological sections were matched to electrophysiological recording data by matching tissue artifacts, probes and lesions placed during the mapping experiments. Injections in both PV and S2 were confined to the field of interest. For PV, the injection of WGA-HRP in one case (A) was centered in the representations of the hand and face, but likely spread into the representation of the oral structures. In another case, the injection of WGA-HRP was centered in the bilateral representation of the upper ventral trunk and proximal forelimb (B). In S2, an injection of WGA-HRP was centered in the representation of the forelimb in the left hemisphere (C) and an injection of fluororuby was centered in the expected location of the forelimb/hand and face in the right hemisphere (D): (▲) face; (○) forelimb; (□) foot; (●) hand; (△) shoulder; (■) trunk. Other conventions are as in previous figures.

thalamus, the lateral and medial divisions of the ventral posterior nucleus (VPl and VPm) could be readily defined because of their darkly staining appearance and high packing density observed in sections stained for Nissl substance (Fig. 3B). These nuclei are even more striking in sections reacted for CO, since, they are very darkly staining compared to surrounding nuclei of the thalamus (Figs. 3A and 4C). The inferior division of VP (VPi) resides just ventral to VPl and VPm and is a very sparsely packed nucleus that stains very lightly for CO (Fig. 4 B). The superior division of the VP superior nucleus (VPs) is densely packed with darkly stained cells, like VP proper, but can be distinguished from the latter by its moderately dark appearance in sections stained for CO.

The anterior pulvinar (Pla) is a nucleus that contains very small cells that are moderately packed. At middle levels of the thalamus, this nucleus resides just lateral to the centre médian nucleus (CM), dorsal to VP and medial to VPs, and at posterior levels, dorsomedial to the posterior nucleus (Po) and lateral to the pretectum (PT). Other nuclei of interest include the mediodorsal nucleus (MD) and the lateral posterior nucleus (LP). MD is divided into a medial, magnocellular division (MDm) which contains large, darkly staining cells, a parvocellular division (MDp) which resides lateral and ventral to MDm and contains smaller cells, and a far lateral multiform nucleus which resides medial to the central lateral nucleus (CL) (as shown in Jones, 1998 for complete description). In our preparation, the Nissl stains allowed us to determine the borders of MDm and MDp. However, the multiform division was difficult to distinguish. In sections stained for CO, MD could be distinguished from other surrounding nuclei (Fig. 5 A), and the magnocellular division

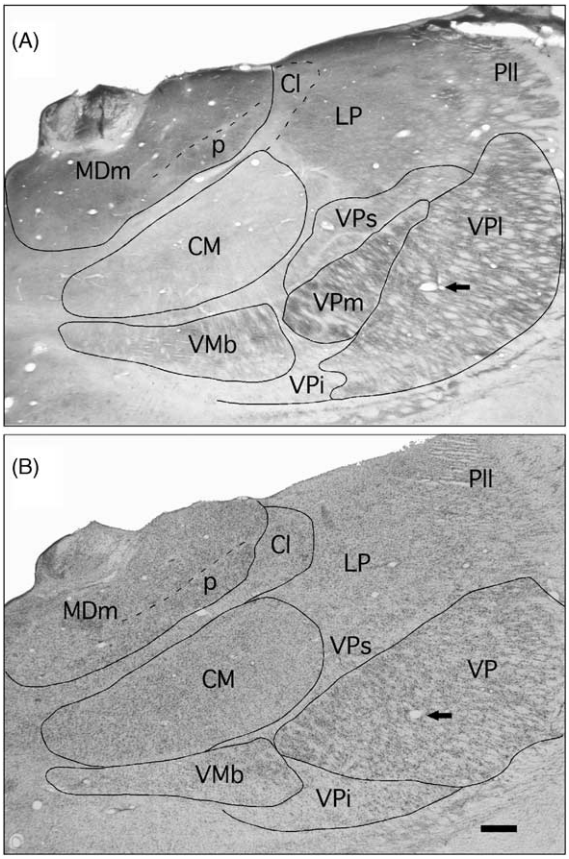

Fig. 3. Lightfield photomicrographs of adjacent, coronally sectioned tissue through the middle level of the thalamus that have been stained for (A) CO or (B) Nissl. A number of thalamic nuclei can be readily identified at this level in both preparations including MD, VP, VPi, CM, and VPs. Within the MD nucleus, a central magno- and a lateral parvo-cellular division can be distinguished in both types of staining. Arrow marks the same blood vessel. Dorsal is to the top and lateral is to the right. Scale bar equals 1 mm.

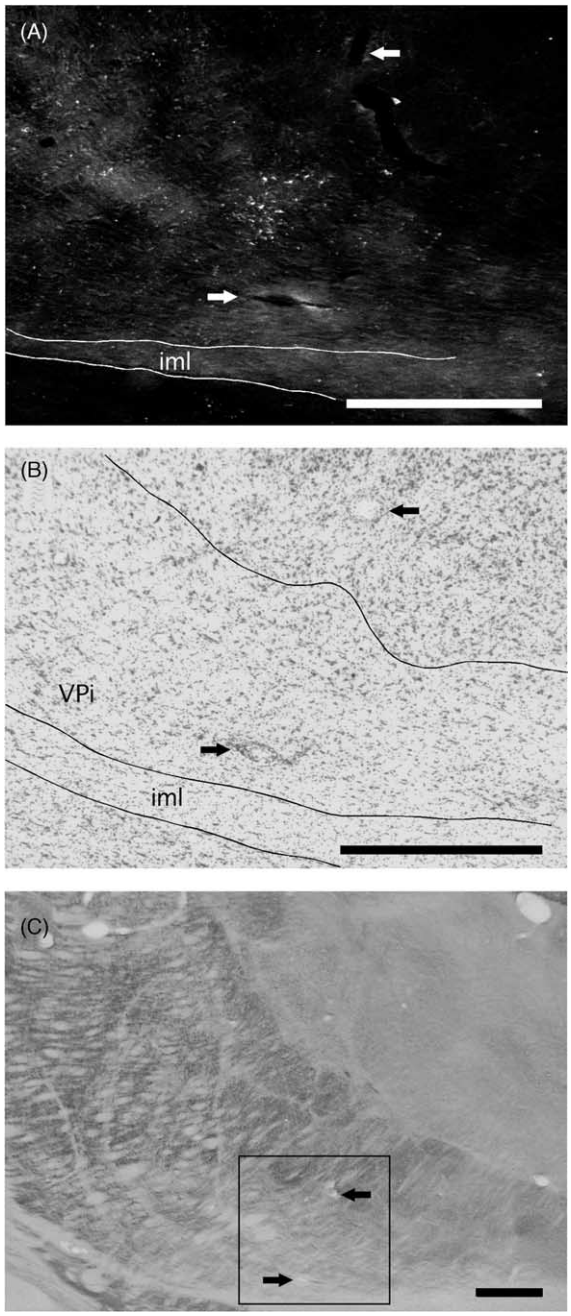

Fig. 4. (A) Darkfield and (B and C) lightfield digital images of adjacent thalamic sections taken from middle levels of the thalamus in case 99-6L. Labeled cell bodies and axon terminals were located in a dense cluster in (A) VPi. Location was determined by matching blood vessels (arrows in all figures) across sections. In (B) Nissl stained sections, VPi contains small, very lightly packed cells compared to the larger, darkly staining and densely packed cells in VPm. In (C) tissue that was stained for CO, VPi is lightly staining compared to the dorsally located VPl and VPm. Other conventions are as in previous figures.

within MD stained somewhat lighter than the parvocellular division. The LP is a relatively homogenous nucleus containing moderately packed cells. This nucleus resides dorsal to VPs and Pla, and is found at posterior and middle levels of the thalamus.

3.3. *Thalamocortical connections of PV and S2*

In two cases, injections of WGA-HRP were placed into electrophysiologically identified body part representations in PV and labeled cell bodies and axon terminals were related to architectonically defined nuclei of the thalamus (Figs. 4A, 5A, 6 and 7). In both cases, Pla, VPi, and MDm had dense interconnections with PV. Labeled cell bodies and axon terminals were found in a dense focus in Pla and VPi. In one case, the label in MDm was in a dense focus (99-6; Fig. 6), and in the second case there was a scattering of cells at the ventral portion of the nucleus (98-1; Fig. 7). In this same case, MDp also contained a scattering of cells. In one case, the injection site appears to have spread into the representation of the oral structures in PV. In this case, a small cluster of label was also observed in VMB, a nucleus generally associated with gustation (as shown in Jones, 1985; Fig. 6). Finally, labeled cells in one case were observed in

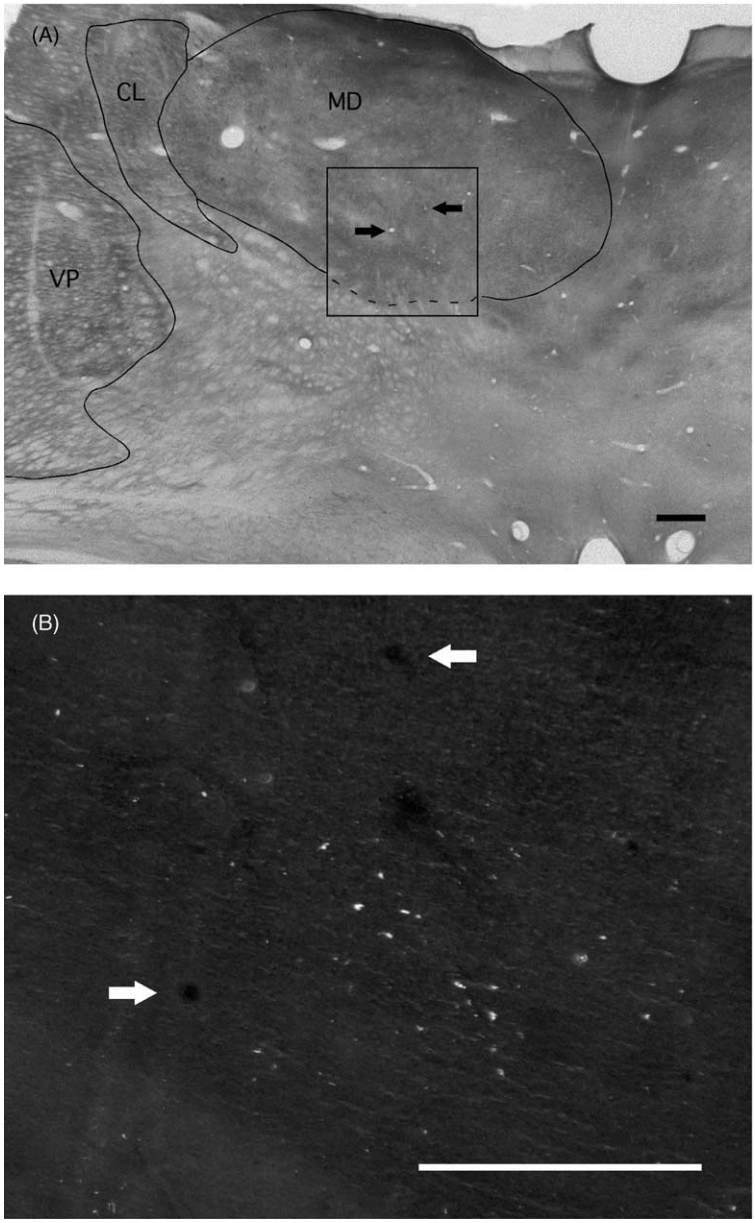

Fig. 5. (A) Lightfield and (B) darkfield digital images taken from rostral levels of the thalamus in case 99-6L. Labeled cells resulting from an injection into the hand and face representation of PV were observed in the MDm. MDm stains darkly for CO and Nissl.

CL and LP (99-5). In the case in which an injection was centered in the bilateral representation of the upper ventral trunk (98-1) labeled cell bodies and axon terminals were similar in location and pattern to the other injection, and found only in the ipsilateral thalamus (Figs. 2B and 7).

Connections of S2 were examined in two cases (Fig. 2 C and D). Both cases resulted in highly restricted patterns of label in VPi, VPs, and Pla (Figs. 8 and 9). Unlike PV, no label was observed in MD or CL. Although the body part representation was different for each of the injection sites in S2 and PV, the pattern of label did not appear to vary with respect to the topographic organization of the thalamic nuclei.

4. Discussion

In the present investigation we have shown that in the Old World macaque monkey, PV receives input from VPi, Pla and MDm, which is interconnected with prefrontal cortex, entorhinal cortex and the amygdala (e.g. Porrino et al., 1981; Goldman-Rakic and Porrino, 1985; Russchen et al., 1987; see Ray and Price, 1993 for review). Injections in PV inconsistently labeled VMB, MDp, and CL. S2 receives input from Pla, VPi and VPs. The latter two nuclei are associated with processing deep inputs from the muscles and joints as well as vestibular input (Fig. 10).

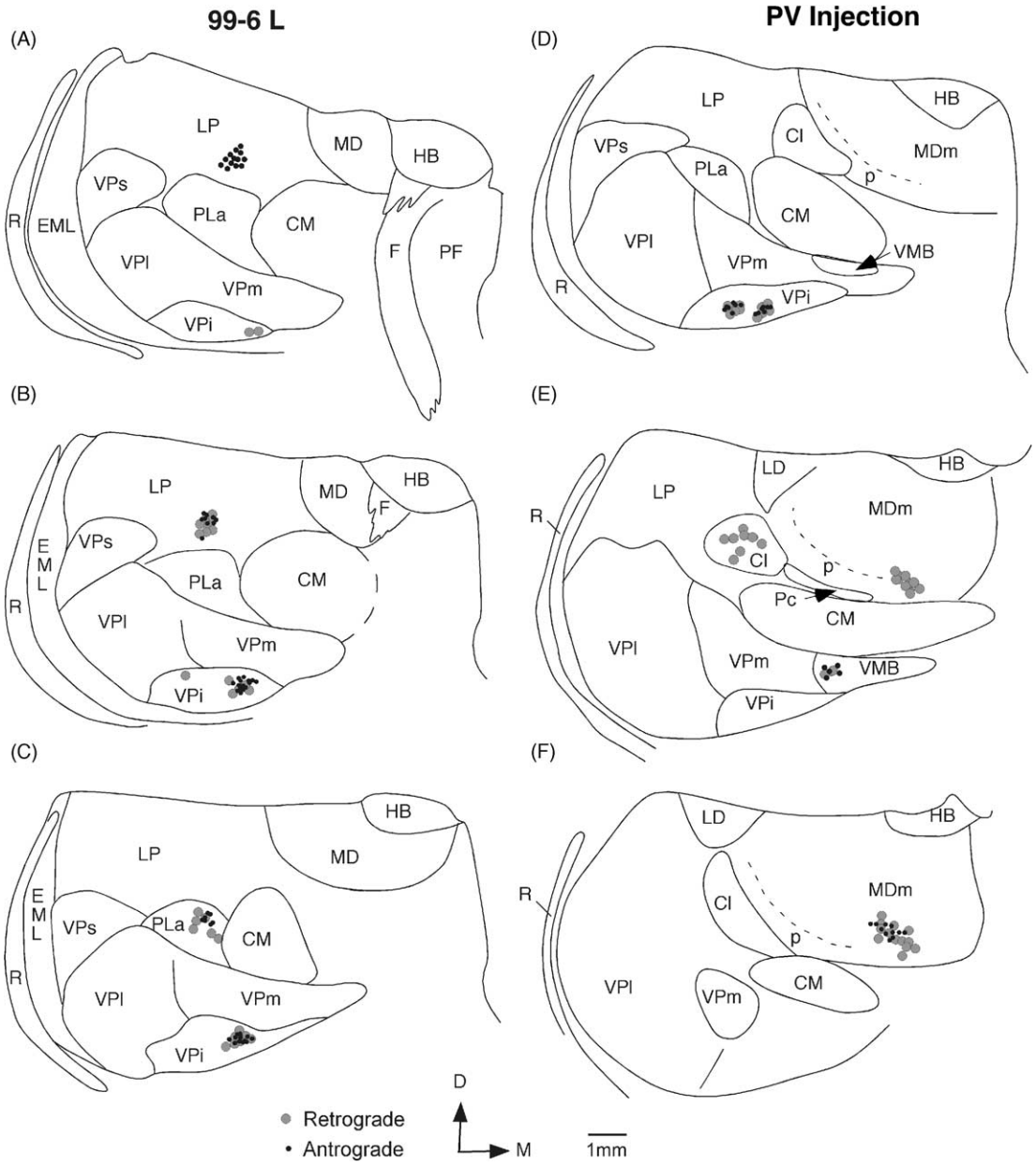

Fig. 6. Reconstruction of labeled cell bodies and axon terminals following an injection of WGA-HRP into the hand and face representation of PV in case 99-6 L (see Fig. 2 A). Transported tracer was observed in several nuclei including VPi, Pla, LP, MD, CL and VMB. Conventions as in previous figures.

Currently, our understanding of the specific patterns of connections of the different cortical fields in the lateral sulcus of primates, including S2, is based on only a few studies. There are two studies in which injection sites in S2 were electrophysiologically defined (Burton and Carlson, 1986; Krubitzer and Kaas, 1992), one study in which the injection sites were small and appeared to be limited to architectonically defined S2 (Friedman and Murray, 1986), and one study in which injections sites in both PV and S2 were electrophysiologically defined (Krubitzer and Kaas, 1992).

Our results are similar to these previous studies, and the patterns of thalamic label are largely consistent across primates. In studies of macaque monkeys in which small injections were placed in the expected location of S2, labeled cell bodies were identified predominantly in VPi, Plo (our Pla), and CL (Friedman and Murray, 1986). Interestingly, injections that were displaced slightly rostral and medial to the S2 region, in the expected location of PV, resulted in additional label in the MD, much like our injections in PV. In studies of non-human primates in which injection sites in S2 were electrophysiologically identified, the results are also similar (Burton and Carlson, 1986; Krubitzer and Kaas, 1992). In marmosets, injections in S2 resulted in labeled cell bodies and axon terminals in VPi and Pla. Although no label

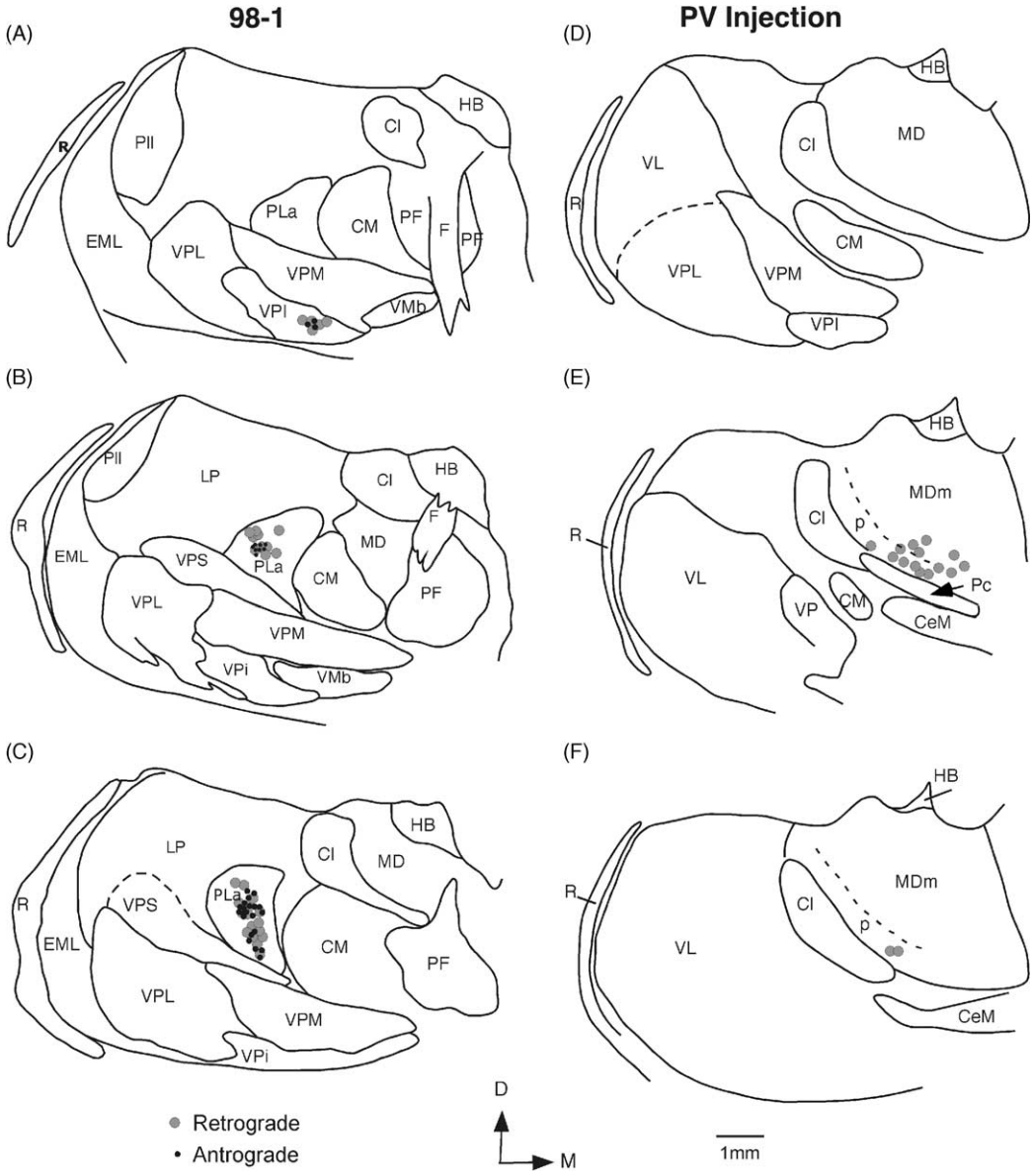

Fig. 7. Reconstruction of labeled cell bodies and axon terminals following an injection of WGA-HRP into the bilateral representation of the upper ventral trunk and proximal forelimb representation of PV in case 98-1 (see Fig. 2 B). Transported tracer was observed in VPi, Pla, and MD. Conventions as in previous figures.

was identified in VPs, as in the present investigation, the size of Pla in the marmoset in the previous study was large, and may actually have included portions of VPs. In galagos, S2 received input from VPl, VPi, Po and CL (Burton and Carlson, 1986). It is possible that some of the variation observed in the galago, particularly the projection from VPl, reflects true species differences. Another possibility is that the variability in the projection patterns in the galago versus the marmoset and macaque monkey arises from inconsistent identification of thalamic nuclei across studies (see Huffman and Krubitzer, 2001 for review of this issue).

While there are other investigations in which thalamocortical connections of the S2 region were examined in primates either by placing injections on the upper bank of the lateral sulcus, or placing injections in the thalamus (e.g. Jones and Powell, 1970; Burton and Jones, 1976; Mufson and Mesulam, 1982; see Jones, 1985, 1998 for review), the results of these studies are difficult to interpret for two reasons. First, the injection sites in the S2 region were often large and could have been in one of any number of different cortical areas that reside in the lateral sulcus (e.g. see Robinson and Burton, 1980a,b; Cusick et al., 1989; Krubitzer et al., 1995a; Disbrow et al., 2000 for description of multiple fields in the lateral sulcus). Second, although in some investigations small, restricted anterograde tracer injections were placed in different thalamic nuclei (e.g. Burton and

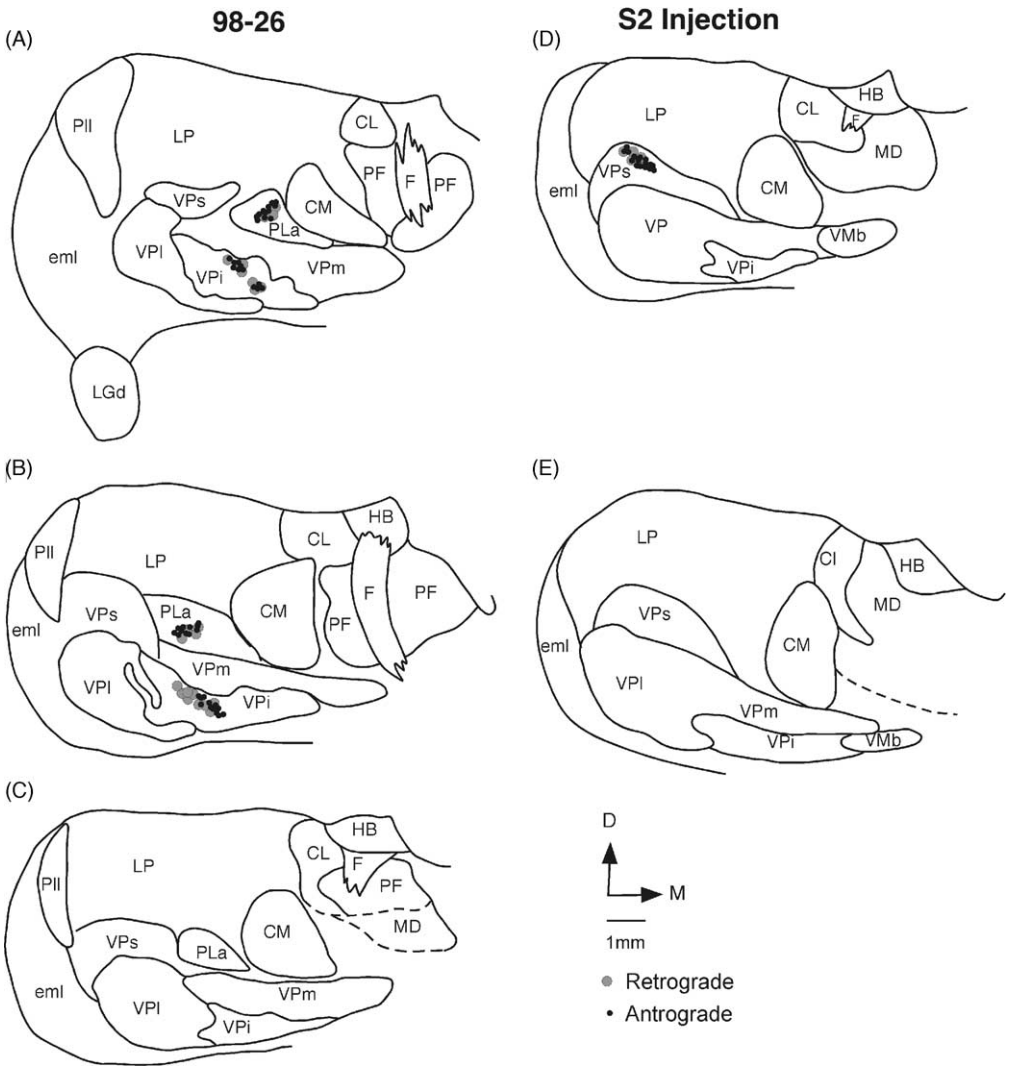

Fig. 8. Reconstruction of labeled cell bodies and axon terminals following an injection of WGA-HRP into the representation of the forelimb of S2 in case 98-26 (see Fig. 2 C). A transported tracer was observed in several nuclei including VPi, Pla, and VPs. Conventions as in previous figures.

Jones, 1976), the specific area in the lateral sulcus to which these nuclei projected was not clearly identified based on modern descriptions of multiple fields in this region.

Thalamocortical connections of PV have only been investigated in the marmoset (Krubitzer and Kaas, 1992). The results of the current study are remarkably similar to those described previously for the marmoset in that the major projections to PV arise from VPi, MD, Pla and LP. Although the pattern of connections suggests that S2 and PV share some functions, the presence of a connection between PV and MD in the present and previous studies indicates that PV may play a unique role in processing somatic inputs. MD is a thalamic nucleus intimately associated with the orbitofrontal and dorsomedial divisions of pre-frontal cortex (Fig. 10; Goldman-Rakic and Porrino, 1985; Ray and Price, 1993). The magnocellular division of MD receives input from prefrontal cortex and a number of other ventral forebrain structures including the amygdala, entorhinal cortex, and olfactory cortex (Porrino et al., 1981; Russchen et al., 1987; see Ray and Price, 1993 for review). In addition, all divisions of MD receive input from the substantia nigra (Ilinsky et al., 1985; Russchen et al., 1987), and lateral portions of MD (in the location of MDp) receive a number of inputs from the brainstem, including the medial vestibular nucleus. The inputs to MD, and its projection to PV indicate that it may be involved in higher-level perceptual processes and tactile learning and memory (Mishkin, 1979; Murray and Mishkin, 1984; Friedman et al., 1986; Goldman-Rakic, 1990). Further, the inputs from the substantia nigra and vestibular nucleus further implicates this field in sensorimotor integration, and head rotation and velocity (as mentioned below).

With the exception of the galago, a consistent observation across primates is that PV and S2 receive little if any direct input from the ventral posterior nucleus proper of the thalamus (Fig. 10). The lack of input from VP indicates that all cutaneous drive of neurons in S2 and PV arises via

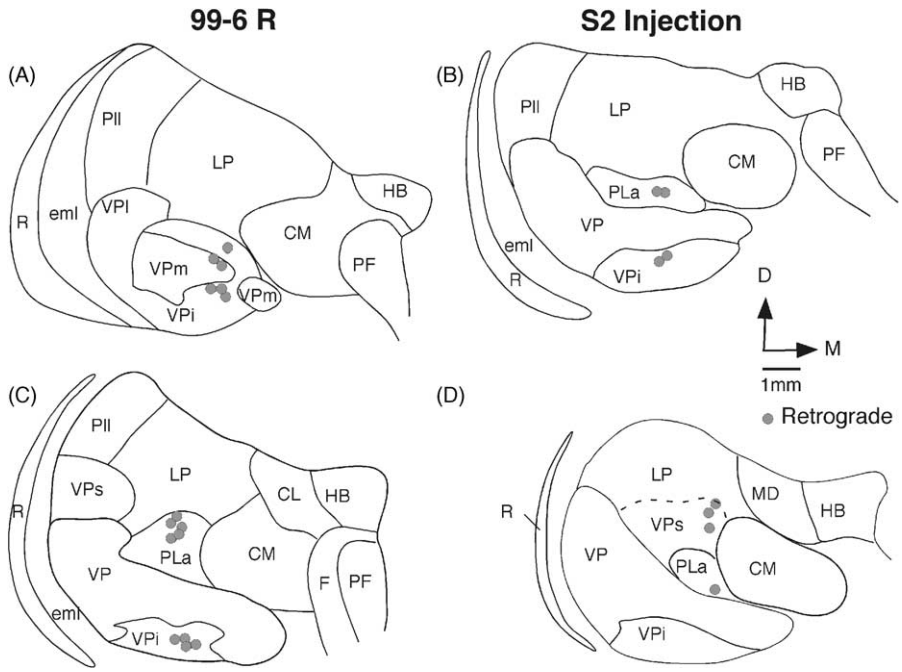

Fig. 9. Reconstruction of labeled cell bodies following an injection of flouroruby into the expected location of the forelimb representation of S2 in case 99-6 R (see Fig. 2 D). A transported tracer was observed in VPi, Pla, and LP. Conventions as in previous figures.

corticocortical connections from anterior parietal fields. This supposition is supported not only by connection studies that indicate that areas 3b and 1 project to the S2 region (including S2 and PV, e.g. Jones and Powell, 1969; Darian-Smith et al., 1993; Cusick et al., 1989; Krubitzer and Kaas, 1990; Burton et al., 1995; see Kaas and Pons, 1988 for review), but also by ablation studies. In macaque and marmoset monkeys, ablation of areas 3b and 1, or the anterior parietal strip, abolishes the responses of neurons in S2 to cutaneous stimulation (Pons et al., 1988; Garraghty et al., 1990; Pons et al., 1992). While it has been suggested that cooling area 3b does not reduce evoked potentials to cutaneous stimulation in S2 (Zhang et al., 1996), in fact 72% of individual neuronal responses were either reduced or abolished in that study. This inconsistency may be related to the fact that S2 was not clearly defined, that responses from neurons in more than one field may have been measured, or that cooling did not completely de-activate 3b.

4.1. The role of PV and S2 in sensorimotor integration and tactile discrimination

Several of the thalamocortical connections observed in the present investigation support the role of PV and S2 in tasks which require somatic and motor integration, such as object manipulation, bimanual exploration, object identification, and active reaching. First, connections of PV and S2 with VPi indicate that these areas have access to information from deep receptors, such as muscle spindles and Golgi tendon organs. VPi receives its primary sources of input from the dorsal column nuclei, the principal division of the trigeminal nucleus, the lateral cervical nuclei and the spinothalamic tract (as shown in Kaas and Pons, 1988 for review). Neurons in VPi respond to stimulation of Pacinian corpuscles (Dykes et al., 1981; Kaas et al., 1984), as well as to stimulation of deep receptors, muscle stretch and limb displacement (Loe et al., 1977; Dykes et al., 1981; Krubitzer et al., 1995b). One would predict that the discrimination involved in judgements of object length, size, and shape would require information about the state of muscle stretch and load across the various muscles of the digits, palm, and even the forelimb.

S2 also receives input from VPs. Like VPi, neurons in VPs or the region of VPs (the shell of VPLc, see Jones, 1998) respond to stimulation of deep receptors (Dykes et al., 1981; Jones and Friedman, 1982; Krubitzer et al., 1995b). VPs receives input from the semicircular canals via the medial vestibular nucleus (Lang et al., 1979; see Fukushima, 1997 for review). The projection from this nucleus to S2 further implicates S2 in proprioception, or the knowledge of the relative position of the limbs in space and head rotation. Connections of both S2 and PV with the Pla are difficult to interpret because little is known about the subcortical inputs to this nucleus (see Jones, 1998). For example, one study (e.g. Rausell and Jones, 1991) demonstrates that there are sparse projections to this nucleus from the spinal division of the trigeminal nucleus, which is generally associated with crude touch and pain. However, these inputs only comprise a small portion of the entire nucleus. Limited electrophysiological recording in this nucleus indicates that neurons here respond to both deep and cutaneous stimulation (Loe et al., 1977). Studies of cortical connections indicate that this

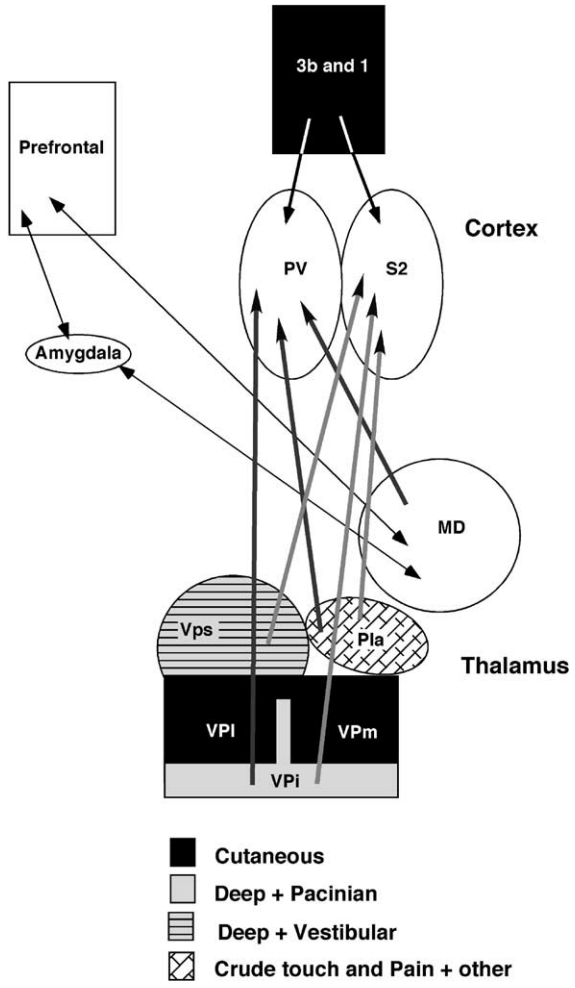

Fig. 10. A summary of the major thalamic connections of S2 and PV in macaque monkeys. The afferent inputs and neural responses of projecting nuclei indicate that both S2 and PV are involved in sensory motor integration. The prefrontal–amygdala–MD circuit, and its interface with PV indicate that PV may be involved in tactile, learning, memory and cognition. Conventions as in previous figures.

nucleus is generally associated with the somatosensory system because it receives input from a number of somatosensory fields (e.g. Jones et al., 1979; Yeterian and Pandya, 1985).

More recent data in our laboratory indicates that PV is part of a sensory-motor processing network of several cortical fields involved in coordinated movements, particularly within and between the hands. We recently described a cortical field rostral to PV in the macaque monkey that responds to somatosensory stimulation that we call the rostral lateral (RL) area (Disbrow et al., 2000). Cortico-cortical connection data from the macaque monkey demonstrate that PV has dense connections with RL (Disbrow et al., 1998). FMRI studies indicate that RL is not consistently active under passive tactile stimulation, but is active in tasks that have a motor component, such as squeezing and grasping (Hinkley et al., 2001). Further, both S2 and PV have an increase in the number of active voxels and an increase in magnetic field strength at long latencies resulting from bilateral versus unilateral stimulation of the hand (Disbrow et al., 2001). Taken together, the data implicate both S2 and PV in somatic and motor integration necessary for tasks involving object manipulation with one or both hands, object identification and goal directed reaching and grasping. Further, PV may be involved in tactile learning, memory and cognition.

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References

Beck, P.D., et al., 1996. Topography, architecture, and connections of somatosensory cortex in opossums: evidence for five somatosensory areas. J. Comp. Neurol. 366, 109–133.

Burton, H., Jones, E.G., 1976. The posterior thalamic region and its cortical projection in New World and Old World monkeys. J. Comp. Neurol. 168, 249–302.

Burton, H., Carlson, M., 1986. Second somatic sensory cortical area (SII) in a prosimian primate, *Galago crassicaudatus*. J. Comp. Neurol. 24, 200–220.

Burton, H., et al., 1995. Cortical areas within the lateral sulcus connected to cutaneous representations in areas 3b and 1: a revised interpretation of the second somatosensory area in macaque monkeys. J. Comp. Neurol. 355, 539–562.

Burton, H., et al., 1997. Tactile-spatial and cross-modal attention effects in the second somatosensory and 7b cortical areas of rhesus monkeys. Somatosens. Mot. Res. 14, 237–267.

Burton, H., et al., 1999. Tactile attention tasks enhance activation in somatosensory regions of parietal cortex: a positron emission tomography study. Cereb. Cortex 9, 662–674.

Carroll, E.W., Wong-Riley, M.T.T., 1984. Quantitative light and electron microscopic analysis of cytochrome oxidase-rich zones in the striate cortex of the squirrel monkey. J. Comp. Neurol. 2221–2217.

Cusick, C.G., et al., 1989. Somatotopic organization of the lateral sulcus of owl monkeys: area 3b, SII and a ventrolateral somatosensory area. J. Comp. Neurol. 282, 169–190.

Darian-Smith, C., et al., 1993. Ipsilateral cortical projections to areas 3a, 3b, and 4 in the macaque monkey. J. Comp. Neurol. 335, 200–213.

Disbrow, E., et al., 1998. Cortical and thalamic connections of the parietal ventral area (PV) in macaque monkeys. Soc. Neurosci. Abstr. 24, 130.

Disbrow, E., et al., 2000. Somatotopic organization of cortical fields in the lateral sulcus of *Homo sapiens*, evidence for SII and PV. J. Comp. Neurol. 418, 1–21.

Disbrow, E., et al., 2001. Evidence for interhemispheric processing of inputs from the hands in the human second somatosensory and parietal ventral areas. J. Neurophysiol. 85, 2236–2244.

Dykes, R.W., et al., 1981. Regional segregation of neurons responding to quickly adapting, slowly adapting, deep and Pacinian receptors within thalamic ventroposterior nuclei in the squirrel monkey (*Saimiri sciureus*). Neuroscience 6, 1687–1692.

Forss, N., Jousmäki, V., 1998. Sensorimotor integration in human primary and secondary somatosensory cortices. Brain Res. 781, 259–267.

Friedman, D.P., Murray, E.A., 1986. Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque. J. Comp. Neurol. 252, 348–373.

Friedman, D.P., et al., 1986. Cortical connections of the somatosensory fields of the lateral sulcus of macaques: evidence for a corticolimbic pathway for touch. J. Comp. Neurol. 252, 323–347.
Fukushima, K., 1997. Corticovestibular interactions: anatomy, electrophysiology, and functional considerations. Exp. Brain Res. 117, 1–16.
Gallyas, F., 1979. Silver staining of myelin by means of physical development. Neurology 1, 203–209.
Garraghty, P.E., et al., 1990. Ablations of areas 3b (SI proper) and 3a of somatosensory cortex in marmosets deactivate the second and parietal ventral somatosensory areas. Somatosens. Mot. Res. 7, 125–135.
Gibson, A.R., et al., 1984. A sensitive low artifact TMB procedure for the demonstration of WGA-HRP in the CNS. Brain Res. 298, 235–241.
Goldman-Rakic, P.S., 1990. Cellular and circuit basis of working memory in prefrontal cortex of non-human primates. Prog. Brain Res. 85, 325–336.
Goldman-Rakic, P.S., Porrino, L.J., 1985. The primate mediodorsal (MD) nucleus and its projection to the frontal lobe. J. Comp. Neurol. 242, 535–560.
Hinkley, L.B., et al., 2001. Somatosensory and motor integration in the human sylvian fissure. Soc. Neurosci. Abstr. 27, 48.11.
Hsiao, S.S., et al., 1993. Effects of selective attention on spatial form processing in monkey primary and secondary somatosensory cortex. J. Neurophysiol. 70, 444–447.
Huffman, K.J., Krubitzer, L., 2001. Thalamo-cortical connections of areas 3a and M1 in marmoset monkeys. J. Comp. Neurol. 435, 291–310.
Huffman, K., et al., 1999. The organization of somatosensory cortex in three species of marsupials, *Dasyurus hallucatus*, *Dactylopsila trivirgata*, and *Monodelphis domestica*: neural correlates of morphological specializations. J. Comp. Neurol. 403, 5–32.
Huttunen, J., et al., 1996. Significance of the second somatosensory cortex in sensorimotor integration: enhancement of sensory responses during finger movements. Neuroreport 7, 1009–1012.
Ilinsky, I.A., et al., 1985. Organization of the nigrothalamocortical system in the rhesus monkey. J. Comp. Neurol. 236, 315–330.
Jones, E.G., 1985. The Thalamus. Plenum Press, New York.
Jones, E.G., 1998. The thalamus of primates. In: Bloom, F.E., Bjorklund, A., Hokfelt, T. (Eds.), Handbook of Chemical Neuroanatomy, the Primate Nervous System, Part III, Elsevier, Amsterdam, pp. 1–298.
Jones, E.G., Powell, T.P.S., 1969. Connexions of the somatic sensory cortex of the rhesus monkey. Part I. Ipsilateral cortical connections. Brain 92, 477–502.
Jones, E.G., Powell, T.P.S., 1970. Connexions of the somatic sensory cortex of the rhesus monkey. Part III. Thalamic connexions. Brain 93, 37–56.
Jones, E.G., et al., 1979. Differential thalamic relationships of sensory-motor and parietal cortical fields in monkeys. J. Comp. Neurol. 183, 833–882.
Jones, E.G., Friedman, D.P., 1982. Projection pattern of functional components of thalamic ventrobasal comple somatosensory cortex. J. Neurophysiol. 48 (2), 521–544.
Kaas, J.H., Pons, T.P., 1988. The somatosensory system of primates. Comp. Primate Biol. 4, 421–468.
Kaas, J.H., et al., 1984. The somatotopic organization of the ventroposterior thalamus of the squirrel monkey, *Saimiri sciureus*. J. Comp. Neurol. 226, 111–140.
Krubitzer, L.A., Kaas, J.H., 1990. The organization and connections of somatosensory cortex in marmosets. J. Neurosci. 10, 952–974.
Krubitzer, L.A., Calford, M.B., 1992. Five topographically organized fields in the somatosensory cortex of the flying fox: microelectrode maps, myeloarchitecture, and cortical modules. J. Comp. Neurol. 317, 1–30.
Krubitzer, L.A., Kaas, J.H., 1992. The somatosensory thalamus of monkeys: cortical connections and a redefinition of nuclei in marmosets. J. Comp. Neurol. 319, 123–140.
Krubitzer, L., et al., 1995a. A redefinition of somatosensory areas in the lateral sulcus of macaque monkeys. J. Neurosci. 15, 3821–3839.
Krubitzer, L.A., et al., 1995b. Cortical connections from physiologically defined nuclei of the somatosensory thalamus of macaque monkeys. Soc. Neurosci. Abstr. 21, 1757.
Krubitzer, L.A., et al., 1986. Microelectrode maps, myeloarchitecture, and cortical connections of three somatotopically organized representations of the body surface in the parietal cortex of squirrels. J. Comp. Neurol. 250, 403–430.
Krubitzer, L., et al., 1998. Interhemispheric connections of somatosensory cortex in the flying fox. J. Comp. Neurol. 402, 538–559.
Lang, W., et al., 1979. Vestibular projections to the monkey thalamus: an autoradiographic study. Brain Res. 177, 3–17.
Lin, Y.-Y., et al., 2000. Differential effects of muscle contraction from various body parts on neuromagnetic somatosensory responses. NeuroImage 11, 334–340.
Loe, P.R., et al., 1977. Body representation in ventrobasal thalamus of macaque: a single-unit analysis. J. Neurophysiol. 40, 1339–1355.
Mesulam, M., 1978. Tetramethyl benzidine for horseradish peroxidase neurohistochemistry: a non carcinogenic blue reaction-product with super sensitivity for visualizing afferents and efferents. J. Histochem. Cytochem. 26, 106–117.
Mishkin, M., 1979. Analogous neural models for tactual and visual learning. Neuropsychologia 17, 139–151.
Mufson, E.J., Mesulam, M., 1982. Insula of the Old World monkey. Part II. Afferent cortical input and comments on the claustrum. J. Comp. Neurol. 212, 23–37.
Murray, E.A., Mishkin, M., 1984. Relative contributions of SII and area 5 to tactile discrimination in monkeys. Behav. Brain Res. 11, 67–83.
Penfield, W., Rasmussen, T., 1968. Secondary sensory and motor representation. In: The Cerebral Cortex of Man. A Clinical Study of Localization of Function. Hafner Publishing Company, New York (Chapter VI).
Pons, T.P., et al., 1988. Lesion-induced plasticity in the second somatosensory cortex of adult macaques. Proc. Natl. Acad. Sci. U.S.A. 85, 5279–5281.
Pons, T.P., et al., 1992. Serial and parallel processing of tactual information in somatosensory cortex of rhesus monkeys. J. Neurophysiol. 68, 518–527.
Porrino, L.J., et al., 1981. Direct and indirect pathways from the amygdala to the frontal lobe in rhesus monkeys. J. Comp. Neurol. 198, 121–136.
Rausell, E., Jones, E.G., 1991. Chemically distinct compartments of the thalamic VPM nucleus in monkeys relay principal and spinal trigeminal pathways to different layers of the somatosensory cortex. J. Neurosci. 11, 226–237.
Ray, J.P., Price, J.L., 1993. The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in macaque monkeys. J. Comp. Neurol. 337, 1–31.
Robinson, C.J., Burton, H., 1980a. Somatotopographic organization in the second somatosensory area of *M. fascicularis*. J. Comp. Neurol. 192, 43–67.
Robinson, C.J., Burton, H., 1980b. Organization of somatosensory receptive fields in cortical areas 7b, retroinsula, postauditory. J. Comp. Neurol. 192, 69–92.
Russchen, F.T., et al., 1987. The afferent input to the magnocellular division of the mediodorsal thalamic nucleus in the monkey, *Macaca fascicularis*. J. Comp. Neurol. 256, 175–210.
Sinclair, R.J., Burton, H., 1993. Neuronal activity in the second somatosensory cortex of monkeys (*Macaca mulatta*) during active touch of gratings. J. Neurophysiol. 70, 331–350.
Steinmetz, P.N., et al., 2000. Attention modulates synchronized neuronal firing in primate somatosensory cortex. Nature 404, 187–190.
Whitsel, B.L., et al., 1969. Symmetry and connectivity in the map of the body surface in somatosensory area II of primates. J. Neurophysiol. 32, 170–183.
Woolsey, C.N., 1958. Organization of somatic sensory and motor areas of the cerebral cortex. In: Harlow, H. F., Woolsey, C. N., (Eds.), The

Biological and Biochemical Bases of Behavior. University of Wisconsin Press, Madison.

Woolsey, C.N., Fairman, D., 1946. Contralateral, ipsilateral, and bilateral representation of cutaneous receptors in somatic areas I and II of the cerebral cortex of pig, sheep, and other mammals. Surgery 19, 684–702.

Yeterian, E.H., Pandya, D.N., 1985. Corticothalamic connections of the posterior parietal cortex in the rhesus monkey. J. Comp. Neurol. 237, 408–426.

Zhang, H.Q., et al., 1996. Parallel processing in cerebral cortex of the marmoset monkey: effect of reversible SI inactivation on tactile responses in SII. J. Neurophysiol. 76, 3633–3655.