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THE MEDULLARY SOURCES OF PROJECTIONS TO THE KINESTHETIC THALAMUS IN THE RACCOON

By

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ABSTRACT

THE MEDULLARY SOURCES OF PROJECTIONS
TO THE KINESTHETIC THALAMUS IN RACCOONS

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Kinesthetic receiving regions in the medulla are known to project to cerebellum, but the medullary sources of projections to the kinesthetic thalamus are not known. The purposes of these studies were to 1) establish the distribution of cells projecting to the thalamus in comparison with that of cells projecting to the cerebellum; and 2) establish the cells of origin of the kinesthetic projections to the thalamus. We used the retrograde transport of horseradish peroxidase, either injected via a microliter syringe (for large injections into either the thalamus or cerebellum) or expressed from a simultaneous recording/injecting electrode (for small injections into the kinesthetic thalamus) in 25 raccoons.

Seven nuclear subdivisions in the dorsal medulla were recognized. In 1) the central cluster region of the cuneate-gracile complex, in 2) cell group z and 3) the reticular portion of cell group x, 85-95% of the cells project to the thalamus as do 30% of the cells in 4) the basal subdivision of the cuneate. In the compact portion of cell group

x, 30% of the cells project to the ipsilateral and 30% to the contralateral cerebellum. Both the contralateral thalamus and ipsilateral cerebellum receive projections from: equal numbers of cells (20%) in 5) the rostral cuneate subdivision; 6) the external cuneate and 7) its medial tongue project predominantly to the cerebellum (72 and 62% of the cells respectively) with 10%-20% projecting to the thalamus. In the kinesthetic thalamus, projections from cell group z and the reticular portion of x are found lateral to those from the external cuneate-medial tongue and basal cuneate. Electrophysiological mapping of the dorsal medulla confirmed that all these nuclear subdivisions projecting to the kinesthetic thalamus receive projections from the deep tissues of the body, primarily from the forelimb.

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ABBREVIATIONS

bCu	basal region of the cuneate n.
Ca	caudate n.
cCu	cluster region of the cuneate n.
cg	cell group
CGr	central grey of the midbrain
Cu	cuneate n.
CuGr	cuneate-gracile nuclear complex
da	area receiving projections from the deep tissues of the arm
DCN	dorsal column nuclei
df	area receiving projections from the deep tissues of the leg
ECu	external cuneate n.
FA	fast adapting response
Gr	gracile n.
H	area receiving projections from cutaneous receptors in the head
Hc	heterogenous area of SI cortex
HRP	horseradish peroxidase
IC	inferior colliculus
IFT	infratrigeminal n.
KVB	kinesthetic subdivision of the ventrobasal complex
L	area receivng projections from cutaneous receptors in the leg
LCN	lateral cervical n.

LGN lateral geniculate n.

MAc muscle afferent region of the SI cortex

MB mammillary body

Mc primary motor area of cortex

Mt medial tongue extension of the ECu

rCu rostral region of the cuneate n.

RN red n.

SA slowly adapting response

SI primary somatosensory area of the cerebral cortex

VA ventroanterior n. of the thalamus

VB ventrobasal complex of the thalamus

Vc glabrous skin representation area of SI cortex

VL ventrolateral n. of the thalamus

VLc ventrolateral n., caudal part

VPI ventroposteroinferior n.

VPLc ventroposterolateral n., caudal part

VPLo ventroposterolateral n., oral part

VPM ventroposteromedial n.

x-c cell group x, compact part

x-r cell group x, reticular part

5,4 area receiving projections from cutaneous receptors in the

3,2 indicated digits of the hand

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CHAPTER I. LITERATURE REVIEW

INTRODUCTION

Elucidating the principles of structural organization and how this organization may relate to the function of the central nervous system is one of the primary goals of neuroscience. The hypothesis that a segregation of projections into functional subunits, within which the elements respond to single stimulus submodalities, which exist at each level (or synapse) of the ascending somatosensory system is garnering increasing experimental support. Data suporting this organizational principle has been most extensively studied at the most easily accessible level of this three level system, the cerebral cortex. At the preceding levels, from which the cortex receives its information (and perhaps derives its organization) much less is known of the organization of the sensory thalamus and relatively little of this organization at the medullary level.

CORTICAL CYTOARCHITECTONIC ORGANIZATION

To preface a discussion of cortical functional organization, a brief description of the architectonic organization of sensory and motor cortex is necessary. Traditionally, these two cortical regions are considered to be separated by the central sulcus. with the motor cortex rostral and the sensory cortex caudal (Johnson '80). Precentral cortex or area 4 (that region lying anterior to the central sulcus) can be characterized by the presence of giant pyramidal cells in layer V. Postcentral cortex or area 3b can be characterized by an expanded granular layer IV as well as the presence of the outer layer of Baillarger (the cell free stripe between layers IV and V). These

designations were described by Brodmann ('03) in man and primates and by Hassler & Muhs-Clement ('64) in cats. In the depths of the central sulcus lies an area (designated 3a) which is cytoarchitecturally characterized as the transition zone between the giant pyramidal cells in layer V of area 4 and the attenuation of the granular layer IV of the sensory cortex (Jones & Porter '80). There appears to be a variable degree of species specific overlap of these cytoarchitectural features (see Jones & Porter '80). In human cortex (Brodman '03), new world monkeys (Bonin '38, Jones '75, Sanides '68) and cats (Hassler & Muhs-Clement '64) there is some overlap; in old world monkeys (Jones, Coulter & Hendry '78, Jones, Wise & Coulter '79) and raccoons (Johnson, Ostapoff & Warach '82) there is no overlap of the giant pyramidal cells of motor cortex and the granular layer of sensory cortex.

FUNCTIONAL ORGANIZATION OF THE SOMATOSENSORY AND MOTOR CORTICES

The classical conceptions of the functional organization of the primary somatosensory cortical areas (SI) have recently come under increased scrutiny. Early workers, using rather large surface electrodes or large "microelectrodes" (approximately 500 um in diameter) with large distances between recording sites, found that in the cerebral cortex there were several areas in which stimulation of the peripheral body resulted in evoked activity (review, Johnson '80). The largest such area has come to be known as the primary somatosensory area, or SI. Further, these evoked responses are organized so that stimulation of adjacent area of the body evokes responses in adjacent loci in the cortex. This functional organization has been termed somatotopy and can be demonstrated in virtually any mammal. Rather

than a single representation of the body surface (Woolsey '58) several laboratories, including our own, using finely detailed micromapping techniques have recently proposed that multiple representations of all or parts of the body in fact exist in SI in a wide variety of species (raccoon; Johnson et al. '82, cat; Dykes, Rasmussan,& Hoeltzell '80; primates, Kaas, Nelson, Sur, Lin, & Merzenich '79, monkey; Zimmerman '68, galago; Sur, Nelson & Kaas '80; tree squirrel, Sur, Nelson, & Kaas '78; opossum, Pubols, Pubols, DiPette & Sheely '76). The most compelling evidence derives from maps of large numbers of electrode penetrations recording evoked activity in single animals in which the pattern of responses recorded in closely spaced electrode penetrations describe not a single somatopic representation but a split representation. For example, evoked responses from a proximal digit may lie on both sides of the representation of the distal tip of that digit forming a mirror image within which each of these representations appear to maintain somatotopy (e.g. grey squirrels, Sur et al. '78) or the representation of the proximal digit may have on either side representations of the distal digit (owl monkey, Merzenich, Kaas, Sur & Lin '78 or the representations may be found in serial order, i.e. proximal digit, distal digit, proximal digit, distal digit as in Rhesus monkey (Paul, Merzenich and Goodman '72).

These multiple body representations may be segregated on the basis of response characteristics (presumably related to stimulus submodality, i.e. cutaneous slow and fast adapting, deep, pacinian, etc.).

The pattern of physiological responses one obtains when recording from these cortical areas adjoining the central sulcus remains fairly

constant. Most rostral is the classical primary motor cortex (area 4) in which stimulation of cutaneous and muscle· afferents may evoke physiological responses (Murphy, Wong & Kwan '75, Lucier, Ruegg & Wiesendanger '75, Hore, Preston, Durkovic & Cheney '76). Its primary physiological feature is the low threshold this cortex displays for electrical stimulation of muscle movements (Woolsey '58, Hardin, Arumugasamy & Jameson '68). In the rostral part of SI cortex one can record responses from either light tactile peripheral stimulation or from electrical stimulation of cutaneous nerves (this is generally regarded as related to the architectonic cortical area 3b). In between these two regions, often in the depths of the central sulcus, are responses to peripheral stimulation of the deeper lying tissues or to electrical stimulation of the muscle afferent nerves, (usually considered area 3a (monkey: Phillips, Powell & Wiesendanger '71, Merzenich et al. '78; cat: Kaas et al. '79). Recently interest has focussed on this cortical region (3a) lying mainly in the depths of the central sulcus because it responds short latency to muscle Ia afferents (Phillips et al. 1971) and lies between the classical sensory cortex (area 3b) and motor cortex (area 4).

Area 3a is not the only cortical cytoarchitectonic area receiving muscle afferent input in monkeys. Area 4, in conscious monkeys, also responds to peripheral stimulation (Lemon '79, Tanji & Wise'81 , Wise & Tanji '81). Area 2 in monkeys, also considered a part of S1, receives muscle afferent information (Merzenich et al. '78) as does the SII cortex (Andersson, Landgren and Wolsk '66). We have not, however, recorded unit responses to peripheral stimulation in the motor cortex (Area 4) in anesthetized raccoons (Johnson et al. '82) nor have we

investigated the caudal SI area for muscle afferent input (analogous to area 2 in the monkey).

THALAMO-CORTICAL RELATIONSHIPS

It has, of course, long been known that the primary sources of input to the cerebral cortex are via the dorsal thalamus (Poliak '32). In general it has been found that (using the terminology developed in the carnivore thalamus) the ventrobasal complex innervates the SI sensory cortex and the ventrolateral complex innervates the motor cortex.

Thalamic Nomenclature

A brief discourse on the various thalamic nomeclatures in necessary both to accurately define the regions of interest to this study as well as to provide a basis for comparisons between published reports on different species. Recently an attempt has been made in this regard (Jones '81) but a more detailed description of the particular thalamic region included in this study appears necessary. Thalamic nomenclature has historically proceeded from the parcellation and naming of nuclei on the basis of the distribution pattern of cell bodies (Nissl cytoarchitectonics) or of myelinated fibers (myelo-architectonics), often with little data concerning the connectivity or functional characteristics of the regions being studied. Only later was experimental demonstration that these architectonic divisions represent functional subunits provided as a basis for defining nuclear regions (often leading to another classification scheme). This has of course led to confusion in

nomenclature especially as regards analagous nuclei in different species.

Carnivores. The region of interest to this study, defined by connectivity and physiological function, is the rostral pole of the thalamic region receiving afferent innervation from the somatosensory (via the medial lemniscus) system. In carnivores, an early description of the dog and cat thalamus by Rioch ('29) subdivided the ventral nucleus of the dorsal thalamus into several subdivisions. The subdivisions of interest here are, in order of their appearance in transverse sections from rostral to caudal: n. ventralis anterior, n. ventralis pars medialis, n. ventralis pars externa, n. ventralis pars arcuata. Briefly the defining cytoarchitectural characteristics of each of these are:

n. ventralis anterior- this forms the rostral pole of the ventral nucleus. Caudally there are large polygonal cells which are distributed between horizontally running fibers.

n. ventralis pars medialis- this forms the medial portion of the ventral nucleus and extends in its caudal portions dorsolaterally to cap the n. ventralis p. arcuata. The cells are medium sized and polygonal with no large cell bodies.

n. ventralis externa- the cellular characteristics in this division include a mixture of very large cells similar to those in n. vent. anterior and small elongated ones in the anterior regions of this nucleus. The nucleus lies in the ventrolateral part of the middle of the ventral nucleus more or less surrounded by the n. ventralis pars arcuata.

n. ventralis pars arcuata- this comprises the main portion of n. ventralis and is roughly semilunar in shape, hence the name. It is said to contain three types of cells. 1) those similar to n. ventralis anterior. 2) small and medium cells similar to 1) but lighter staining and smaller. 3)cells similar to the largest in n. ventralis externa.

By 1952 a simplified scheme, based on available experimental data was being used by Rose and Mountcastle in which the ventral nucleus of the thalamus was subdivided into essentially three "complexes"; the ventrolateral (VL, comprisng the n. ventralis anterior (VA) of Rioch. This was thought to receive a major input from the cerebellum (via the superior cerebellar peduncle) and project to motor cortex; the ventrobasal complex (VB, including the n. ventralis pars externa and pars arcuata) as these nuclei received a major input from the medial lemniscus and spinothalamic pathways and that the region of thalamus responding to tactile stimulation was coextensive with these nuclei; and the ventromedial complex (including the n. ventralis medialis) which was distinguished by a lack of connectional data as well as unresponsiveness to tactile stimulation.

Primates. The nomenclature used in primates is different from that for carnivores. However analogies based on connectivity and physiological function may be drawn. The region of interest to this study in carnivores lies at the border between the thalamic areas receiving cerebellar input and projecting to motor cortex (VL complex) and the area receiving medial lemniscus input and projecting to somatosensory cortex (VB complex). In monkeys the corresponding nuclei, using the nomenclature of Olszewski ('52), are n.

ventroposterolateralis pars oralis (VPLo) and n. ventrolateralis pars caudalis (VLc) for the VL complex (Tracey, Asanuma, Jones & Porter '80, Thatch & Jones '79) and n. ventroposterolateralis pars caudalis (VPLc) and n. ventroposteromedalis (VPM) for the VB complex (Mountcastle & Henneman '52, Berkley '80, Boivie '78, and Kalil '81). Remarkably, the cytoarchitectonic descriptions of these nuclei (Olszewski '52) in primates are in close accord to those corresponding areas in carnivores (Jones et al. '79, Sakai '82).

Thalamocortical Connections

Area 4 (motor cortex) is reciprocally connected only to the VL complex (cats, Jones & Burton '74; raccoons, Sakai '81) or the equivalent region in monkey, VPLo and VLc (Jones et al. '79, Tracey et al. '80), portions of which nuclei can also be characterized by receiving deep cerebellar nuclear projections (Thatch & Jones '79, Hendry, Jones & Graham '79, Kalil '81).

The central portions of SI (area 3b) are reciprocally connected to the central core of the VB complex (monkey: Lin, Merzenich, Sur & Kaas '79; cat: Jones & Powell '68, Jones & Leavitt '73).

The thalamic cells projecting to cortical area 3a are to some extent known in monkeys and cats. Jones et al. ('79) and Friedman & Jones ('81) have shown that area 3a, responding to nerve stimulation of muscle Ia afferents, projects to a "shell" region of VPLc extending from the anterior pole throughout the anteroposterior extent of the dorsal aspect of this nucleus.

In contrast, area 2 (which also receives muscle afferent information) may project only to the caudal part of this shell

(Friedman & Jones '81).

In monkeys, deep pressure stimuli activated single unit discharges in both VPLo and VPLc (Horne & Porter '80, Horne & Tracey '79; Loe, Whitsel, Dreyer & Metz '77; Poggio & Mountcastle '63).

The cervico- and spinothalamic projections appear to project to both the VB (VPLc) and VL (VPLo-VLc) in monkeys (Jones & Powell '68) and cats (Berkley '80).

Thalamic Submodality Segregation

Evidence for the segregation of stimulus submodalies in the thalamus is quite scanty. Early studies did not achieve a sufficiently high resolution (i.e. closely spaced electrode penetrations) nor were the response characteristics observed in such a way as to detect submodality differences (e.g. Rose & Mountcastle '52, Mountcastle & Henneman '52, Welker & Johnson '65). Recently a study satisfying these criteria has been reported using squirrel monkeys (Dykes, Sur, Merzenich, Kaas & Nelson '81). These authors were able to show discrete segregation of two of four response characteristics (fast and slow adapting cutaneous, pacinian and deep) in the VPLc and the ventroposteroinferior n. of the squirrel monkey. Deep responses were segregated dorsally and pacinian responses ventrally (VPI) while the two cutaneous stimulation response categories were mixed in the central core of VPLc in a complex fashion. Also, in the macaque monkey, Maendly, Ruegg, Wiesendanger, Wiesendanger, Lagowski & Hess ('82) have shown that stimulation of forelimb nerves and muscle pulls results in activation of la muscle afferents in a specific rostrodorsal region of VPLc. Thus there is evidence for a segregated region of VB thalamus

receiving projections from deep tissue including muscles and having connections with cortical area 3a.

MEDULLO-THALAMIC RELATIONSHIPS

Medullothalamic Connections

The projections from the dorsal column nuclei (DCN, cuneate-gracile nuclei) to the thalamus have been studied in the cat and monkey (for reviews see Berkley '80a, Kalil '81, Boivie '81). It is known that the major projection zone of the DCN corresponds to VB (VPLc -VPM in monkey) and not to VL (VPLo). These projection systems have been largely treated as single functional units and therefore only a few studies anatomically tracing specific submodality pathways have been done.

It is known that the region in thalamus which projects to cortical area 3a receives input from the spinothalamic neurons in cats and monkeys (Applebaum, Leonard, Kenshalo, Martin & Willis '79, Berkley, '80, Boivie '78), although the spinothalamic nuclei receive little if any group 1 muscle afferents (Foreman, Kenshalo, Schmitt & Willis '79). Lesions and tritiated amino acid injections into the DCN (cuneate-gracile) result in the dorsorostral portion of VB being lightly if at all labeled (Boivie & Bowman '81, Kalil '81).

Dorsal Sensory Nuclei of the Medulla

Cytoarchitectonic Organization and Connections. The dorsal somatosensory nuclei associated with the post-cranial body in the medulla are the gracile (Gr), medially and the cuneate (Cu) laterally

near the obex. Lying more rostrally is the external cuneate (ECu) nucleus and rostral to the Gr, Cu, and ECu and caudal to the vestibular nuclei are Z and X, two cell groups also associated with the somatosensory system.

Within the Gr and Cu are subunits recognized by some authors on the basis of cytoarchitecture, connectivity and physiological responses. These include:

1) the central "cluster" region. In most mammals, to a varing degree, the cells in the central core of both the Cu and Gr exhibit a specific dendritic and cellular arrangement which gives the appearance of local aggregates of cells separated by thin axonal fascicles, called variously lobules, clusters, bricks, or nests (cat, Kuypers & Tuerk '64, Hand '66; monkey, Albright '78, Albright & Haines '78; raccoon, Johnson, Welker & Pubols '68). These clusters have long been considered the primary thalamic projection region of the dorsal medulla (Lund & Webster '67, Cheek, Rustioni & Trevino '75, Hand & van Winkle '77) and receive the densest innervation from the dorsal root fibers (cats, Rustioni & Macchi '68, Hand '66, Kuypers & Tuerk '64, Keller & Hand '70 ; monkeys, Chang & Ruch '47, Ferraro & Barrera '35, Albright '78, Albright & Haines '78).

2) A caudoventral subunit containing large fusiform cells (Kuypers & Tuerk '64), the so called basal cells. This region receives, in addition to a sparse dorsal column input, a cortical input (Kuypers & Tuerk '64, Weisberg & Rustioni '79), a dorsolateral column (spinal) input (Rustioni & Kaufmann '77, Rustioni '74, '77, Rustioni & Molenaar '75, Miller & Basbaum '76).

3) A rostral subunit containing many different sizes and shapes of

cells including some very large ones. These cells are not organized into clusters (Kuypers & Tuerk '64). This region also (like the caudoventral) receives sparse dorsal column innervation, dense dorsolateral column and cortical input (cat: Kuypers & Tuerk '64, Rustioni & Kaufmann '77, Weisberg & Rustioni '79; monkey, Rustioni, Hayes & O'Neill '79). In addition it receives input from other subcortical sources (red nucleus, Edwards '72; reticular formation, Kuypers '60, Sotgui & Marini '77). Some of these cells project to the thalamus but many project to extra-thalamic targets (e.g. cerebellum, Warren, Rowinski, Maliniak, Haring & Pubols '80, Cheek et al. '75, Rinvik & Walberg '75; other brainstem nuclei, Berkley '75, Hand & van Winkle '77; tectum, Berkley & Hand '78, spinal cord, Burton & Loewy '77).

The external cuneate (ECu) nucleus is characterized by the presence of very large multipolar cells located in the dorsolateral aspect of the medulla, rostral to the obex. The ECu receives its major input via the dorsal columns and this input originates in the cervical and upper thoracic dorsal root ganglia (Rustioni & Macchi '68).

Cell groups z and x, first described by Brodal & Pompeiano ('57a) are characterized by their small cell size and varying cell shape (in contrast to the neighboring nuclei except Gr) as well as their connectivity. Cell group x, bordered laterally by the restiform body, rostrally by the descending vestibular nucleus and caudally by the large cells of the ECU does not receive primary vestibular nerve input (as contrasted with the DVN) nor dorsal column input (as contrasted with the ECu) but does receive heavy input from the dorsolateral column (cats: Brodal & Pompeiano '57, Rustioni & Molenaar '75; monkey,

Albright & Haines '78). It projects to the cerebellar cortex and to higher levels of the brainstem (Brodal & Pompeiano '57a, b, Brodal '81).

Cell group z has similar cytoarchitecture to the rostral of the Gr, however is is separated from Gr by a narrow cell free pole strip and receives a major input from the dorsolateral column (cat: Rustioni '74, Rustioni & Molenaar '75; monkey: Albright '78). It projects, not to the cerebellar cortex as does cg x but to the rostral pole of the VB complex (Grant, Boivie & Silfvenius '73).

Physiology. The cluster region of the CuGr is the most heavily studied physiologically. This subunit responds primarily to very light tactile stimulation of the glabrous surfaces of the fore- (Cu) and hindpaws (Gr) (cats, Dykes, Rasmusson, Stretavan & Rehman '82; raccoon, Johnson et al. '68).

The basal region of the CuGr is very difficult to study physiologically. Miller & Basbaum ('76) and Dykes et al. ('82) in cats reported a high number of responses to stimulation of the deep tissues but this was not reported in raccoons (Johnson et al. '68).

The rostral region of these nuclei exhibit larger receptive fields than the cluster region (Kruger, Siminoff & Witkovsky '61, Kruger '61, Perl, Whitlock & Gentry '62, Winter '65, Johnson et al. '68, Dykes et al. '82) and response modality segregation is difficult to detect except in the region where there is a grouping of large cells, similar in appearance to those of the ECu, and these respond to stimulation of the deep tissues in cat (Dykes et al. '82) and raccoon (Johnson et al. '68).

Medullary Submodality Segregation

Recently the hypothesis has been advanced that the segregation of submodalities seen at the cortical and thalamic levels is maintained throughout the ascending somatosensory pathway (Dykes, '82, Johnson et al. '82, Berkley '80). To substantiate this hypothesis, it will be necessary to demonstrate 1) segregation of submodalities in the medulla, and 2) the connections of these segregated regions with the corresponding subunits at the thalamic and cortical levels.

To my knowledge the degree to which submodalities are segregated in the medulla of monkeys has not been investigated using modern techniques although a crude separation of muscle versus cutaneous may been made between the ECu and Cu nuclei. The most recent mapping study of the dorsal medulla in cats (Dykes et al. '82) indicates that there are discrete areas in the dorsal medulla responding in separable ways (i.e. fast adapting versus slow adapting) to cutaneous and deep stimulation. Within the cluster region of the dorsal column nuclei, these authors found that the cutaneous slow adapting (SA) and fast adapting (FA) responses were intermixed (as reported previously by Kruger et al. '61, Gordon & Jukes '64a, b). The deep responses however, were somewhat more segregated. The deep SA responses were limited to the ECu and adjoining rostal subunit of the Cu. The deep FA responses were more diffusely organized and were found in the rostro-medial ECu and the ventral portions of the Cu.

Medullary Muscle Afferent Segregation

Cells in ECu physiologically respond mainly with the fastest

propogated evoked potentials in sensory nerves supplying the muscles of the forelimb and neck (Ia afferents) and project to the ipsilateral cerebellar cortex (Cooke, Larson, Oscarsson & Sjolund '71a, b).

In addition to the ECu, cg z and x have also been reported to respond to electrical stimulation of muscle afferent nerves innervating the periphery of the extremities (both hind and fore limbs. A hindlimb muscle afferent pathway from the medulla to the cerebral cortex of the cat has been described physiologically (Langren & Silfvenius '69, '70, '71). This pathway was said to project from the dorsolateral funiculus via the cg z in the medulla to an ill-defined (stereotaxic coordinates only were given) region of the thalamus to an equally ill-defined region of "sensorimotor" cortex. Jones & Porter ('80) interpreted this cortical area as corresponding to area 3a. Grant, Boivie & Silfvenius ('73), using the Fink Heimer technique following lesions in the dorsal medulla (only one of which was confined to cg z) described the projections of a medullary relay nucleus for muscle afferents to the thalamus. These projections terminated in the caudo-lateral part of VL, immediately adjacent to the rostral dorso-lateral part of VB. Obviously when anyone draws a line on a section describing "the border" between two nuclei (in this case VL and VB) there is some degree of uncertainty. In a more recent article, Hendry et al. ('79) showed that the caudolateral portion of VL does not receive deep cerebellar nuclear input nor does it project to area 4 of the cortex. This region was also identified as analagous to that region receiving spino and cervicothalamic input by another author (Boivie '71a) and not to include regions of VB to which the gracile nucleus (Boivie '71b) and the cervicothalamic fibers (from the lateral cervical nucleus, Boivie

'78) project.

A forelimb muscle afferent pathway to the cortex has also been described physiologically in the cat (Rosen '69a, b, Rosen & Sjolund '73a, b, Rosen & Asanuma '73). Again with scanty histological evidence, it appears that the rostro-ventral portion of the Cu (Oscarsson & Rosen '63) receives muscle afferent projections via the dorsal columns and projects via the thalamus (site undeterminable from these data) to the cerebral cortex (apparently to both preand postcruciate cortex).

Two major problems with these studies (both the hind and forelimb muscle afferent projections) needing resolution are: 1) the majority of these studies are strictly physiological, with recording sites determined by electrical nerve stimulation at the periphery and antidromic electrical stimulation at projection sites. Dykes et al. ('82) state two problems with electrical stimulation of peripheral nerves with regard to the study of stimulus submodality segregation. These were that the axon diameters and conduction velocities overlap so extensively that stimulation of single submodalities in mixed nerves is essentially impossible and that unusual inputs (i.e. those not demonstrable by natural receptor stimulation) can be evoked by electrical stimulation (c.f. Dykes & Gabor '81, Dostrovsky, Jabbur & Millar '78). And 2) histological verification of these projections, preferable with some physiological confirmation of the neuronal responses of the regions experimentally under study is necessary. The meager histology presented in these studies of projection sites consists, at best, of the location of the stimulating electrode, which of course could be activating fibers of passage.

Also the standard mapping procedures using natural peripheral stimulation allow a much larger region to be explored as well as allowing the testing of many submodalities simultaneously. In this fashion, one does not decide a priori which submodality or receptor sites will be studied. Using these methods, it can be said that not only cg z, the rostral Cu and Ecu receive muscle afferent projections but also the ventral and caudal portions of the CuGr (cat: Dykes et al. '82; tree squirrels: Ostapoff, Johnson & Albright '83). Where these latter cells project is now unknown.

Recently Boivie and coworkers described an external cuneothalamic pathway in the monkey. (Boivie, Grant, Albe-Fessard, and Levant '75, Boivie and Bowman '81). The ECN has long been known to receive a massive group 1 afferent input (Cooke et al. '71b). Therefore this pathway is a potential source for the pathway to the muscle afferent rostral cap of the VB thalamus.

From the available evidence it may be hypothesized that the muscle afferent projections, at least some of them, may be segregated within the three levels of the somatosensory system and that this case of submodality segregation may be the most readily demonstrable using current physiological and anatomical techniques.

Significantly, little if anything is known about the brainstem connections to the muscle afferent region in the thalamus of any species.

MUSCLE PROJECTIONS AS THE TESTABLE CASE OF SUBMODALITY SEGREGATION

The muscle afferent projection system has been chosen for study as it appears to be the best candidate for demonstrating submodality

segregation. As mentioned above there is suggestive evidence that evoked responses to stimulation of the deep tissues of the postcranial body occur preferentially clustered together as do responses to stimulation of the skin at each level of the somatosensory system. There are also anatomical distinctions in cortex as well as in the medulla which can be correlated with this response submodality segregation. In addition, it is easier to discriminate between pathways subserving receptors located in the deep tissues and those conveying the cutaneous submodalities than to discriminate between the cutaneous submodalities themselves. The muscle sensory receptors (e.g. golgi tendon organ, muscle spindles, etc) will respond to a variety of stimuli (e.g. deep pressure, joint rotation, muscle stretching, etc.) but as a class they are separable from the majority of the cutaneous receptors on the basis of stimulus intensity. Many muscle sensory receptors respond to deep pressure (substantial indentation of the skin) while most cutaneous receptors respond to very light tactile stimulation (little or no indentation of the skin) in intact preparations. Muscle dissection (e.g. Maendly et al. '81) allows one to selectively stimulate individual muscles and tendons (the connective tissue does however allow for some transfer of the stimulus to neighboring structures). Obviously large scale dissections are inappropriate in experiments in which the animal is expected to recover from the anesthetics for the duration of the survival time and were not used here. The animal cannot remain under the anesthetics during the entire survival time as this inhibits transport (personal observation).

There are three reasons why choosing the muscle afferent stimulation may discriminate submodality pathways better than one of

the cutaneous submodalities. 1) Not all cutaneous receptors have been identified with respect to their response characteristics and adequate stimuli (i.e. the nature of the stimulus which best elicits responses). 2) Those cutaneous receptors which have been adequately described in terms of their response characteristics to specific stimuli show large overlap in both the stimulus which will elicite responses as well as the properties of that response. For instance, pacinian corpuscles follow high frequency, low amplitude sine waves applied to the skin (tuning points in excess of 100-200 Hz) and have broad response fields without distinct boundaries but have an obvious focus of maximal sensitivity (Burgess & Perl '73). Simple dermal corpuscles have a rapidly adapting response to small displacements of the skin but do not follow high frequency stimulation and have small response fields with distinct boundaries (Munger & Pubols '72). There is considerable overlap in stimulus parameters which will activate, albeit not optimally, several classes of receptors (Pubols '80). 3) The projections of the cutaneous submodalities appear to be more complexly organized (i.e. each response subunit appears smaller and the subunits are more intermixed) than do the muscle projections (Dykes et al. '82, Douglas, Ferrington & Rowe '78). The arrangement of the cortical cutaneous subunits also appears to vary considerably from species to species, e.g. the location of the hairy digit representation versus the volar digit representation (c.f. Carlson & Welt '80).

A Segregated Muscle Afferent Pathway Within the Functional Organization of the Raccoon Somatosensory System

Cortex. In the raccoon sensory cortex we have already determined

(Johnson et al. '82) that the functional organization of the rostral reaches of SI in the hand area is organized into three subdivisions. These were designated, in rostrocaudal sequence, MAc (for the area of cortex responding to deep stimulation, including muscle afferents) , Hc (for the area of cortex responding to stimulation of digit claws (one or more) or more than one digit, either hairy or volar stimulation, and Vc (for the area of cortex responding to cutaneous stimulation of the volar forepaw glabrous skin pads and exhibiting a precise detailed somatotopic organization) on the basis of the submodality of the peripheral stimulus necessary to evoke responses. Rostral to the MAc region is the classical motor cortex, Mc (Hardin et al. '68). These designated regions can be roughly correlated with the cortical architectionic areas defined in other species. Thus, area 4 is analagous to Mc; 3a to MAc; and area 3b with Hc and Vc.

Thalamus. More recent work in progress in our laboratory indicates the thalamus of the raccoon, as in the squirrel monkey (Dykes et al. '81) and macaque monkey (Maendly et al. '81), there exists at least a rostral cap to the ventrobasal complex which responds to peripheral stimulation of the deep tissues of the body (including the muscles, Wiener, Johnson & Ostapoff '82). This appears to represent a muscle afferent region segregated from the largely cutaneous representation found ventro-caudally in most of the rest of the VB complex.

Medulla. At the medullary level in raccoons there is also physiological evidence for the segregation of stimulus modality (Johnson et al. '68). Although that study was not designed to

specifically segregate responses on the basis of stimulaus submodality, nonetheless it was noted that the majority of responses to stimulation of the deep tissues of the post-cranial body were segregated spatially to the external cuneate nucleus (ECN) and to a "medial tongue" (MT) of large multipolar cells extending from the ECN medially along the ventral border of the main cuneate nucleus. These nuclear regions may correspond to all or part of the hypothetical medullary muscle afferent area. Separate from these muscle representations, within the cuneate-gracile nuclei (CuGr), responses from stimulation of the volar skin of the hands and feet were found mainly within the central "lobule" regions of the CuGr, while the responses from the claws and hairy skin stimulation were found more externally in the CuGr.

OBJECTIVES OF THESE STUDIES

To begin to understand the functional significance of any system in the brain, detailed information is necessary on the anatomical relationships within that system as well as the physiological properties of each level of organization. It is now known that muscle afferent information reaches various cortical areas, presumably subserving different functions in each area. Further, these cortical areas appear to be reciprocally connected with specific subunits of the ventral nucleus of the thalamus.

At the level of the thalamus, the anatomical and physiological relationships between these subunits are only beginnning to be worked out. The anatomical projections to these thalamic areas are virtually unknown. The body of data describing the physiology of medullary nuclei which may be involved in these pathways is therefore difficult

to interpret, especially in light of the several subunits or areas already known in the thalamus and cortex (best described in the monkey). It is important therefore that specific nuclear groups projecting to discrete, physiologically identified thalamic and cortical subunits be identified. Once the projections from the medulla to cortex via thalamus are known then the physiological characteristics of each of the levels within these pathways may be fully studied: the interactions between levels can be analyzed, and related to the functional significance of each of the separated pathways.

Intra-system submodality segregation may be better demonstrable in raccoons than in other commonly used non-primate species because of the highly elaborated ascending somatic sensory pathway in this animal (Welker & Seidenstein '59, Welker & Johnson '65, Welker, Johnson & Pubols '64, Johnson et al. '68) which is correlated with the raccoon's relatively high manual dexterity (Welker '69).

These experiments were designed to determine the medullary input to one of the segregated zones in the VB thalamus; the one most accessible to study at this time, the segregated zone of projections from deep tissues of the forelimb which includes afferents from the muscles.

Possible Clinical Significance of the Proposed Studies

A potential application of the study of the muscle afferent projection pathway to the cerebral cortex is in the study of Parkinson's Disease induced tremors. Ohye and his co-workers in Japan have been sucessful in controlling drug resistant muscle tremors in humans by placing stereotaxic lesions in a restricted portion of the

thalamus in man, called Vim. This region is characterized by group 1 muscle afferent input and lies near the boundary between VL and VPLc (Cooper, Samra & Bergmann '69, Ohye, Fukamachi, Miyazaki, Isobe, Kakajima & Shibazaki '77). Presently the only animal model available is the monkey (Ohye, Imai, Nakajima, Shibazaki & Hirai '79). It would be of some benefit if an animal such as the raccoon could be developed which had sufficient similarity to the human condition but without the expense of primates in elucidating the anatomical and functional characteristics of the pathway controlling the drug resistant muscular tremors resulting from this disease.

CHAPTER II. COMPARISON OF CELLS IN THE MEDULLA PROJECTING TO THE THALAMUS VERSUS THOSE PROJECTING TO THE CEREBELLAR CORTEX

CHAPTER II. COMPARISON OF CELLS IN THE MEDULLA PROJECTING TO THE THALAMUS VERSUS THOSE PROJECTING TO THE CEREBELLAR CORTEX

INTRODUCTION

The dorsal column nuclei (DCN), at the spino-medullary junction, wherein fibers of the spinal dorsal columns terminate, have been segregated into two major subdivisions according to the destination of their output: the cuneate-gracile nuclear complex (CuGr) projecting to thalamus and the external cuneate nucleus (ECu) projecting to cerebellum. Precise boundaries between CuGr and ECu have never been clear. Some nuclear regions in the vicinity of this vague boundary have been reported to project to both thalamus and cerebellum (in raccoons, Johnson, Welker & Pubols '68, Haring '81, Haring & Rowinski '82). This raises questions about the simple division into two nuclear regions with distinct output pathways. Should we recognize additional subdivisions with diverse outputs? Or is the segregation by output less than total for any of the nuclear subdivisions? Several arrays of further subdivision of the dorsal column nuclei have been proposed, based upon cytoarchitecture, corticobulbar input and connections to and from spinal gray matter.

The purpose of the present study is to establish the distribution of cells projecting to thalamus, in comparison with that of cells projecting to cerebellum, and to relate these distributions to cytoarchitecturally recognizable subdivisions in the dorsal column nuclei of raccoons. Questions concerning projections to other targets (spinal cord, inferior olive, tectum, pretectal nuclei) are not addressed here, and remain for future study.

METHODS

Fourteen raccoons were used in this series of experiments. All animals were imobilized with an intramuscular injection of 1.0 ml (100 mg) Ketamine (Vetalar) to facilitate subsequent anesthetization by intraperitoneal injection of dial (45 mg/kg)-urethane (180 mg/kg). For the thalamic injection group (n=8), the muscles overlying the dorsal skull were retracted and a 75 mm hole bored in the skull to expose the cerebral cortex overlying the thalamus. The head was then positioned and cemented in place in the stereotaxic planes using a special headholder designed to align the center of the external ear canal and the inferior margin of the ocular orbit in the horizontal plane. In each case sufficient exploratory microelectrode mapping penetrations were made in order to determine the position of the Ventrobasal complex (VB). The recording electrode was then replaced by a 5 µl syringe whose tip was lowered to the appropriate coordinates and 1.0-4.0 µl of 20% horseradish peroxidase (HRP, containing approximately equal amounts of Sigma VI, Bohringer-Mannheim type I and Miles brands dissolved in tris buffer pH 8.3 with .025 M KCl and 3% lysophasphotidyl choline) was delivered in 0.1-0.2 µl increments with 5 minutes between increments.

For the cerebellar injection group (n=6) the muscles attached to the occipital pole of the skull were retracted and the cerebellar cortex was exposed from the midline to approximately 1 cm lateral. The skull was then positioned in the stereotaxic planes as before. The needle of the 5 µl syringe was aligned horizontally and introduced into the cerebellum at the vermal-paravermal junction and advanced rostrally to a point lying in the intermediate portion of the anterior lobe

(lobules IV and V). Injection of 1-3.0 µl were made as in the thalamic injections. In addition a series of 3 to 5 smaller surface injections (0.1-0.2 µl each) were made up to 1 mm deep into the dorsal aspect of the paramedian lobule under visual guidance ipsilateral to the anterior lobe injection.

Following injection, all the animals were allowed to survive for 2-4 days (4 days proved optimal for retrograde transport) and then perfused with 500 ml of 0.9% saline followed by 2-4 liters of 1.25% glutaraldehyde, 1% paraformaldehyde in a .1 M phosphate buffer (pH 7.3) followed by 2 liters of 3% sucrose in the phosphate buffer. Brains were removed, blocked and infiltrated at 4 degrees C with 30% sucrose in the buffer for 2-3 days prior to frozen sectioning at 40 or 60 µm in one of the stereotaxic planes. Series of alternate sections were processed with either tetramethylbenzidine (Mesulum & Mufson '80) counterstained with neutral red, or cobalt-intensified diaminobenzidine (Adams '77) counterstained with thionine. All the sections were systematically searched for HRP positive cells at a magnification of 125X and representative sections at five levels through the dorsal sensory medulla were chosen for illustration. The distribution of labeled cells in the dorsal medulla was plotted using a Zeiss drawing tube at a magnification of 50X. These drawings were then transferred to a standardized series of section drawings traken from one animal to facilitate comparisons. Nuclear subregions were based on descriptions of the medulla in the literature of both the raccoon (Johnson et al. '68) and the cat (Kuypers & Tuerk '64, Brodal & Pompieano '57).

In one animal from each group (cerebellar injected and thalamic injected) counts were made of labeled and total numbers of cells within

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In one animal from each group (cerebellar injected and thalamic injected) counts were made of labeled and total numbers of cells within

the nuclear subdivisions recognized in this study in several adjacent sections (3-6). The subregions counted included the cluster, rostral and basal cuneate, the external cuneate and its medial tongue, and the cell group x, compact and reticular portions. No fewer than 115 and up to 300 cells were counted for each sample. The percent of the cells labeled is simply the number of labeled cells divided by the total number of cells. These numbers are used to indicate relative density of projections, not as an absolute number of cells projecting to either the cerebellar cortex or the thalamus.

RESULTS

Subdivisions of the Dorsal Mechanosensory Medulla (Figure 1.1)

Nuclei in the dorsal mudulla reported to receive mechanosensory projections include the Cuneate and Gracile nuclei (CuGr), the External Cuneate nucleus (ECu) and cell groups z and x (cg z, cg x). The CuGr have been further subdivided on the basis of cytoarchitecture (Cajal '09, Kuypers & Tuerk '64, Hand '66, Johnson et al. '68), corticofugal projections (Kuypers & Tuerk '64) and non-primary spinal afferents (Rustioni '74, Rustioni & Molenaar '75).

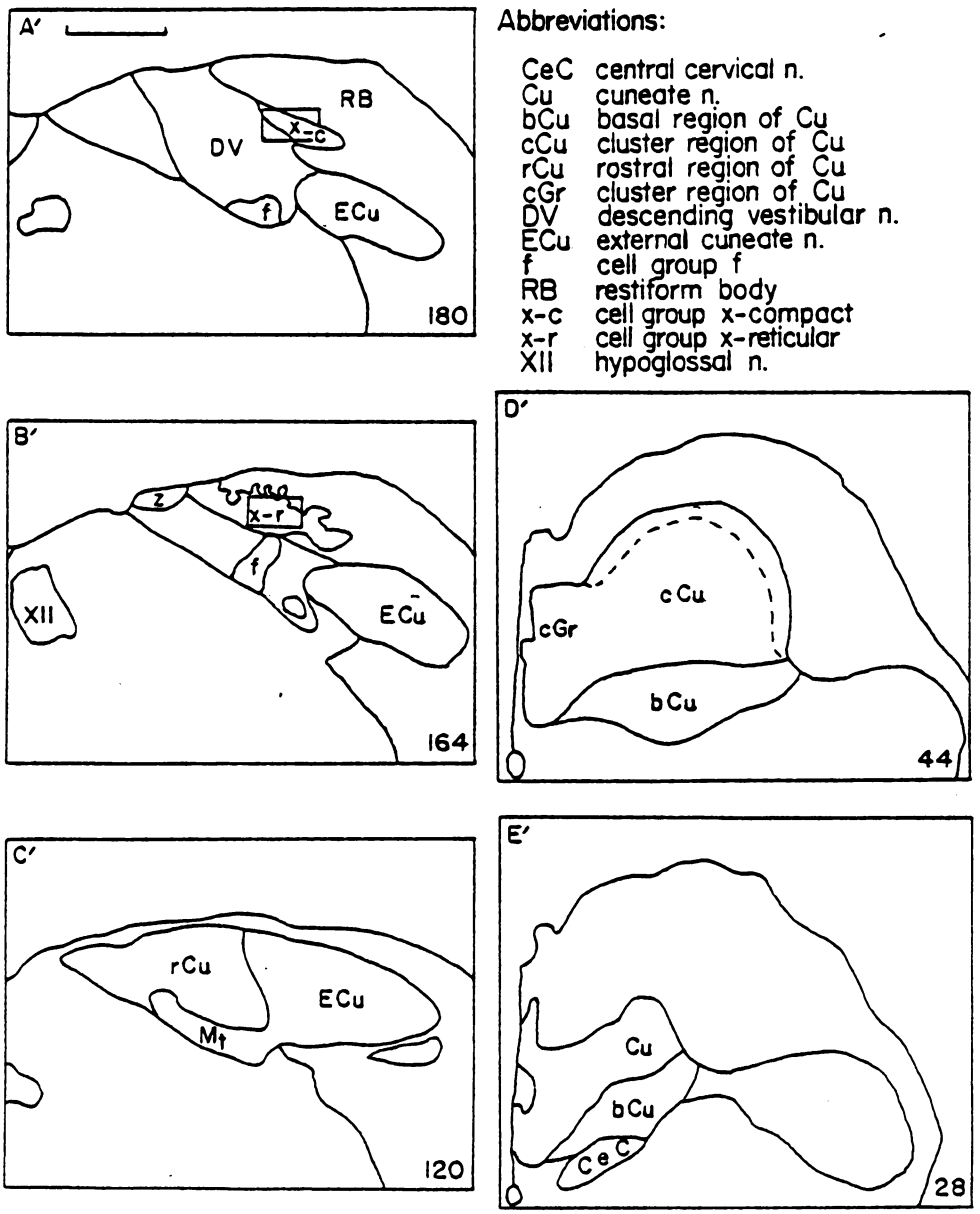
These subregions include a central cell cluster region (cCu) which in the raccoon shows cytoarchitecture and connections to those in the cat (Cajal '09, Kuypers & Tuerk '64, Ellis & Rustioni '81) except that the clusters are very large and well separated by fiber fascicles (Johnson et al. '68).

Other subregions of the CuGr described in the cat apply to the raccoon as well. The rostral pole of the cuneate nucleus (rCu) in

Figure 1.1 Atlas of the nuclear subdivisions of the dorsal mechanosensory medulla.

The nuclear subregions of interest to this study are shown here in these photomicrographs of transverse sections through the dorsal medulla. These are taken from one of the animals receiving a large injection of HRP into the thalamus (animal no. 510L). These frozen sections were reacted with DAB and counterstained with thionine. The levels shown here are approximately those drawn in the summary diagram (Figure 1.12) and their rostrocaudal locations are shown in the inset, top, right. Bar equals 1 mm. A,A'. At a level aproximately 3.5 mm rostral to the obex the tight clustering of cells in cg x-c is apparent lateral and dorsal to the descending vestibular nucleus. Ventral and lateral to the cg x-c is the rostral pole of the ECu. A higher magnification of the area indicated by the box in A' is shown in Figure 1.2 A. B,B'. Approximately one half mm caudal to the previous section the loose arrangement of cells in the cg x-r is seen in approximately the same location. A higher magnification of the area outlined by the box in B' is shown in Figure 1.2 B. C,C'. This section, approximately 1 mm rostral to the obex, shows the rCu, ECu and Mt subdivisions of the DCN. D,D'. The division between the cCu and bCu is quite apparent in this figure taken at a level 1.5 mm caudal to the obex. Note the relative lack of unlabeled cells in the cCu while only some of the cells in the bCu appear labeled. The polymorphous ring external to the cCu is indicated in D' by the dotted line. E,E'. By 2.9 mm caudal to the obex the clustering of cells in the CuGr is much less obvious. This figure shows labeled cells in the caudal portions of the Cu, Gr, bCu and central cervical nuclei.

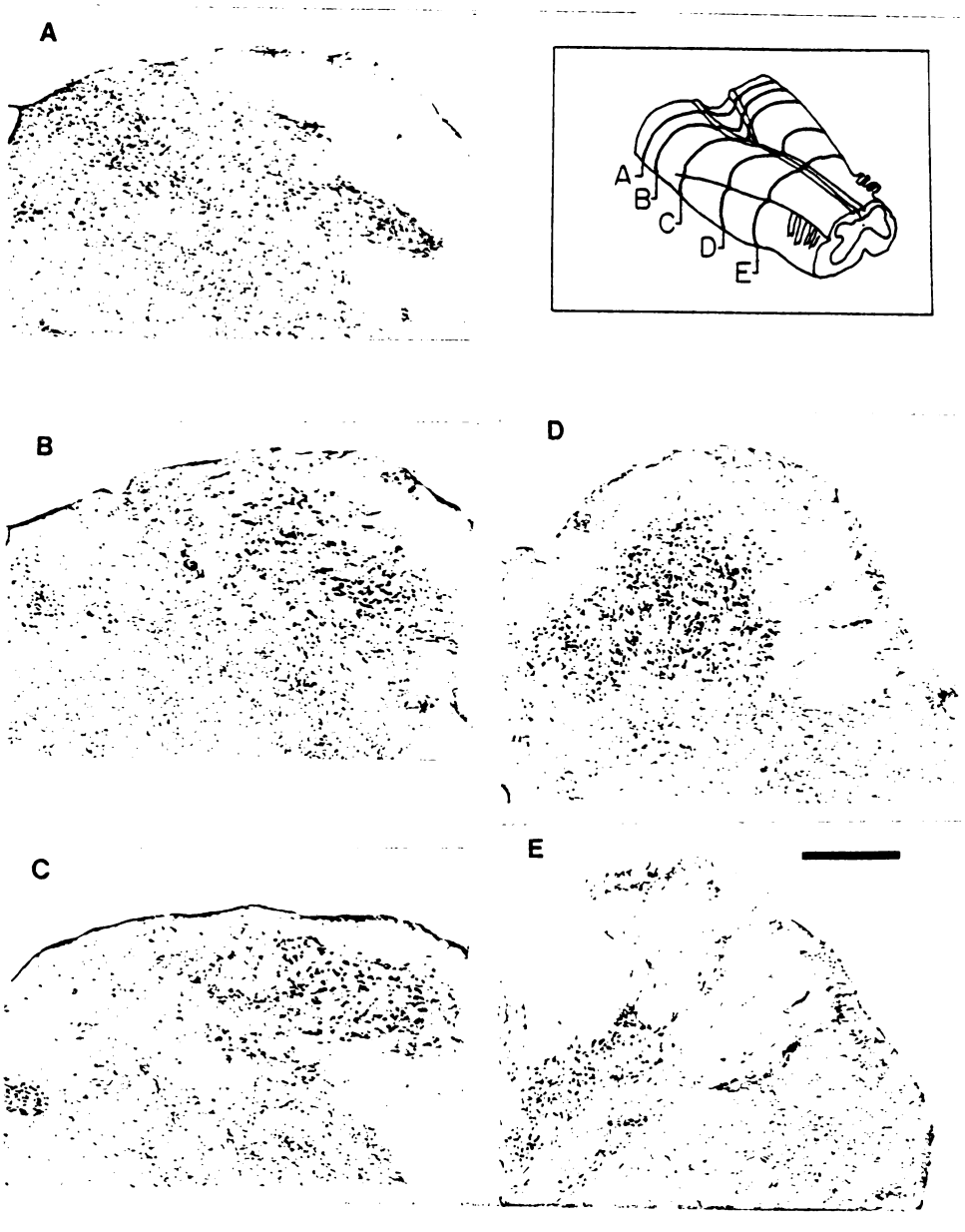
Figure 1.1



Abbreviations:

CeC	central cervical n.
Cu	cuneate n.
bCu	basal region of Cu
cCu	cluster region of Cu
rCu	rostral region of Cu
cGr	cluster region of Cu
DV	descending vestibular n.
ECu	external cuneate n.
f	cell group f
RB	restiform body
x-c	cell group x-compact
x-r	cell group x-reticular
XII	hypoglossal n.

Figure 1.1



raccoon as well. The rostral pole of the cuneate nucleus (rCu) in raccoon is somewhat smaller than that in the cat but as in the cat it contains a polymorphic collection of cell types including large and small triangular, multipolar and fusiform cell bodies (Keller & Hand '70).

Another subregion of the cuneate nucleus of interest here is the basal Cuneate (bCu), the polymorphic region lying beneath the cCu as described in the cat (Cajal '09, Kuypers & Tuerk '64). This region, in contrast to the more dorsal cCu receives corticofugal projections (Kuypers & Tuerk '64) in the cat. Physiological mapping studies in cat (Dykes, Rassmusson, Stretavan & Rehman '82) and raccoon (Ostapoff & Johnson '83c) have shown that this region receives projections from the deep tissues of the forelimb).

Unlike the cat but similar to the monkey (Ferraro & Barrera '35a, b), along the ventral border of the rCu in raccoon is a group of large multipolar cells, similar in morphology and physiological properties to the ECu (Johnson et al. '68, Haring '81, Haring & Rowinski '82) to which this group of cells is connected by a cellular bridge. This cell group was called the medial tongue (Mt) extension of the ECu by Johnson et al. ('68).

Cell groups x and z in the raccoon form a continuous cell zone lying between the vestibular nuclei medial and rostral and the rCu and ECu lateral and caudal. We have subdivided this zone into three parts: cell group z lying caudomedial (cg z), cell group x-reticular (cg x-r) lying intermediate between cg z and cell group x-compact (cg x-c) lying rostrolateral. These subdivisions may also be seen in the cat though cg x-r is much less obvious (personal observation). Cg z in the

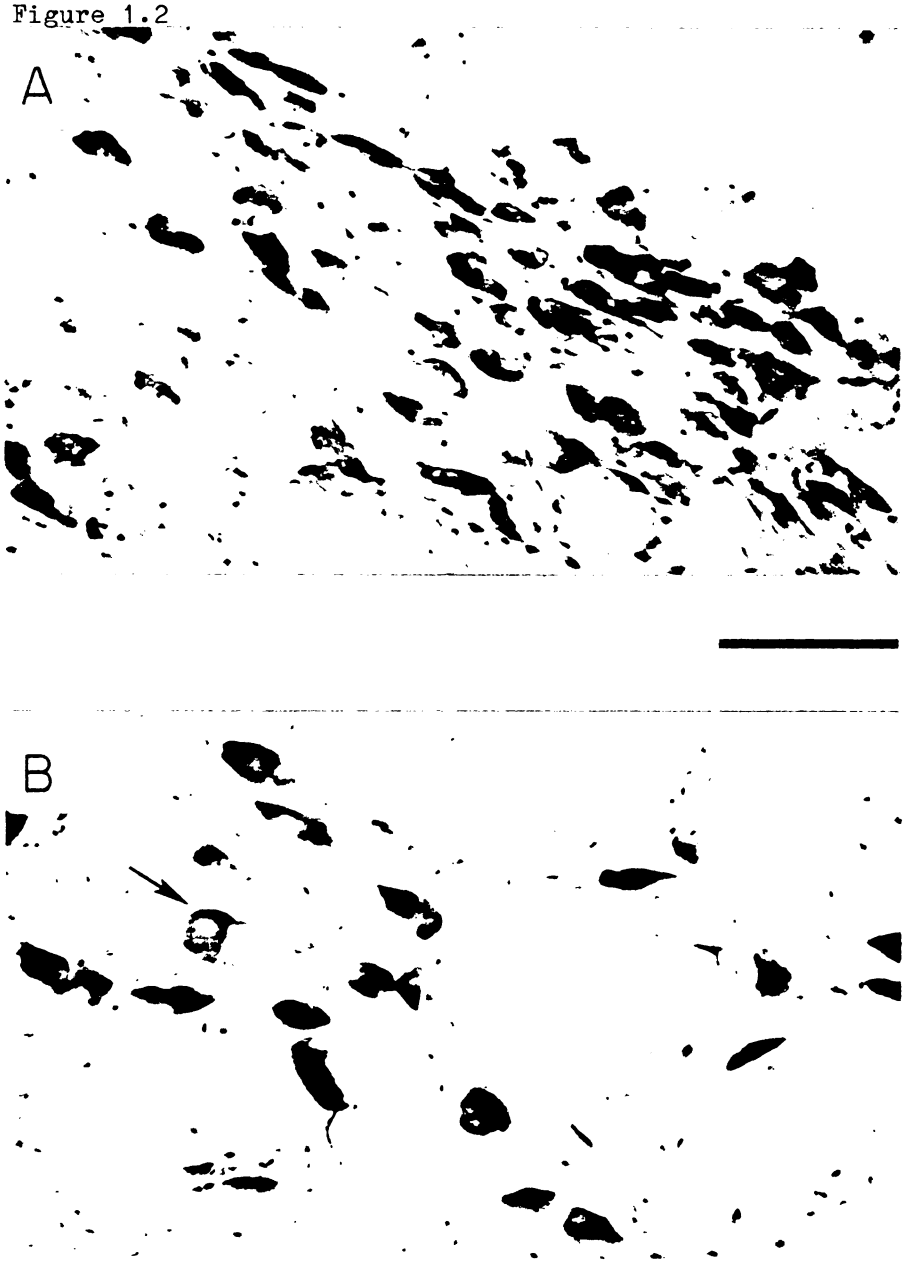
raccoon appears much smaller in mediolateral extent than reported in cat (Brodal & Pompeiano '57a, b) and galago (Albright '78, Albright & Haines '78) though it occupies a similar position just rostral to the Gracile nucleus and caudal to the caudal poles of the medial and descending vestibular nuclei. Cg x is located, as in the cat, dorsal to the rostral pole of the ECu and in raccoon extends medial and caudal, dorsal to the descending vestibular nucleus. In the raccoon two subregions of differing cytoarchitecture are discernable. The mediocaudal two-thirds of the cell group is composed of scattered strings of cells lying within the fibers of the restiform body. This subgroup is here called cg x-r (Figures 1.1B, 1.2B). The rostrolateral one-third of cg x is composed of medium sized cells in a rather more compact arrangement. This subregion more closely resembles the description of cg x given by Brodal & Pompeiano ('57a). It is separated from the rostral ECu (ventrally) by a thin fiber fascicle and in horizontal sections is also separated from the descending vestibular nucleus in a similar manner. We will refer to this subregion as cg x-c (Figures 1.1A, 1.2A).

Stedmann's medical dictionary defines the obex as "the point of the dorsal surface of the medulla oblongata that marks the caudal angle of the rhomboid fossa or fourth ventricle. It corresponds to a small transverse medullary fold overhanging the narrow lower end of the fourth ventricle between the two tuberculum nuclei gracilis" (pp. 973). In the raccoon this bridge of grey matter, bordered caudally by the separation of the two gracile nuclei and rostrally by the merging of the central canal with the fourth ventricle is aproximately 800 μm in the anteroposterior dimension, as measured from 40 μm frozen sections.

Figure 1.2 High magnification photomicrographs to show cytological details of cg x-c and x-r.

A. This is a high magnification photomicrograph (466 X) of the cg x-c taken from the same section as shown in Figure 1.1 A, at the location of the box in Figure 1.1 A'. Dorsal is up and medial to the left. Note that these medium sized cells are closely arranged and separated from the descending vestibular nucleus (bottom, left) by a relatively cell free stripe. B. This is a photomicrograph taken at the same magnification as Figure 1.2 A but from the same section as Figure 1.1 B, at the location of the box in Figure 1.1 B', to show the cells in the cg x-r. These cells appear somewhat larger and are obviously scattered within a fiber bundle. Most of the cells in this photomicrograph show HRP labeling and appear black. One cell (arrow) apears to have a single process labeled (presumably the axon hillock). Bar equals 50 μm.

Figure 1.2



For the purposes of describing the transverse levels illustrated in this paper, the obex, designated 0.0, will refer to any section in this 800 um. Levels rostral to the obex will be designated by a "+" sign followed by the distance from the midpoint of this grey matter bridge. Levels caudal to the obex will be designated by a "-" sign followed by the distance caudal to the midpoint of the bridge.

Medullothalamic Projections

Figure 1.3 presents examples of the thalamic sites of HRP injection. All the injections sites reported for this group were confined to one side of the thalamus and the resultant labeled cells observed in the medulla contralateral to the injection site unless specifically stated.

Labeling Frequency as a Result of Large Thalamic Injections Centered in the Ventrobasal Complex.

A dual labeling pattern of cells in the dorsal sensory medulla was observed following large injections of HRP in the thalamus (Figures 1.4, 1.5). In cg z and x-r (but not cg x-c, Figures 1.6 A, B) and the cluster region of the cuneate and gracile at least 85% of the total number of cells contained HRP reaction product. In addition, the labeling in these nuclei can be characterized as extremely dense, often obscuring the nucleus of the labeled cells. In contrast, the basal and rostral regions of the CuGr showed many fewer cells labeled (less than 30%). The large multipolar cells in the medial two-thirds of the ECu as well as similar cells in the entire Mt also showed relatively light labeling both in terms of frequency of labeled cells and density of

Figure 1.3 Reconstructions of large thalamic injection sites.

Series of sections through the thalamus of two of the animals receiving large thalamic injections of HRP are shown here. The drawing at the top, left depicts a transverse section through the diencephalon with the appropriate locations of the sections drawn in the sagittal (A, 28-141) and horizontal (B, I-IV) planes. On the right (A) is the injection site for animal 510L (see Figure 1.4 for the distribution of labeled cells in the medulla). At the lower left (B) are drawings of horizontal sections showing the injection site in animal 597 (see Figure 1.5 for the distribution of labeled cells in the dorsal medulla in this case). In both animals the dense core of the injection site (as visualized with DAB) includes the entire lateral two-thirds of the thalamus, sparing the midline nuclei as well as the colliculi of the midbrain. DAB-thionine counterstain. The bar equals 1 mm. C. This is a photomicrograph of a sagittal section (28) through the center of the large thalamic injection in animal 510L (see Figure 1.3 A). This section was reacted with DAB and thionine counterstained. Obviously, the entire dorsoventral extent and the rostrocaudal extent of the thalamus to the level of the lateral and medial geniculate nuclei is involved in the injection. Bar equals 1 mm.

Figure 1.3

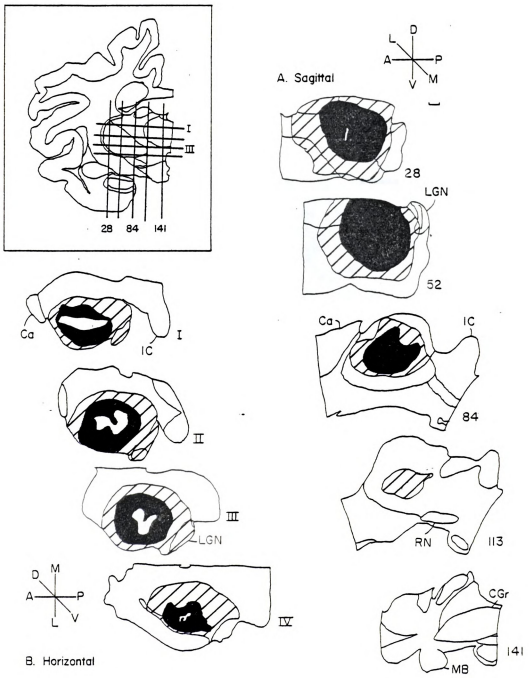

I
III
28
84
141
D
L
A
P
M
V
A. Sagittal
28
LGN
52
Ca
IC
I
II
III
LGN
84
RN
113
CGr
MB
141
IV
B. Horizontal

Figure 1.3

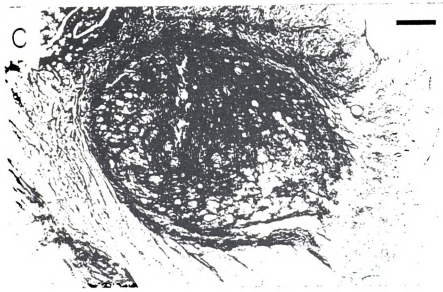


Figure 1.4 Labeling in the dorsal mechanosensory medulla following large thalamic injections.

Shown here is a series of transverse sections through the medulla of animal 510L (Figure 1.3 shows the thalamic injection site). Nuclear subdivisions are indicated by abbreviations. These drawings are taken from the sections shown in Figure 1.1. Nuclear subdivisions which had greater than 85% of the cells labeled (the cg x-r and the cCuGr) are shaded black. The left diagonal shading indicates nuclear areas in which 10-25% of the cells were labeled. These included the bCu, rCu, Mt and Ecu. The vestibular nuclei contained small numbers of labeled cells and these are shown by the dots. Numbered arrows on the right indicate the level of the horizontal sections shown in Figure 1.5. Bar equals 1 mm.

Figure 1.4

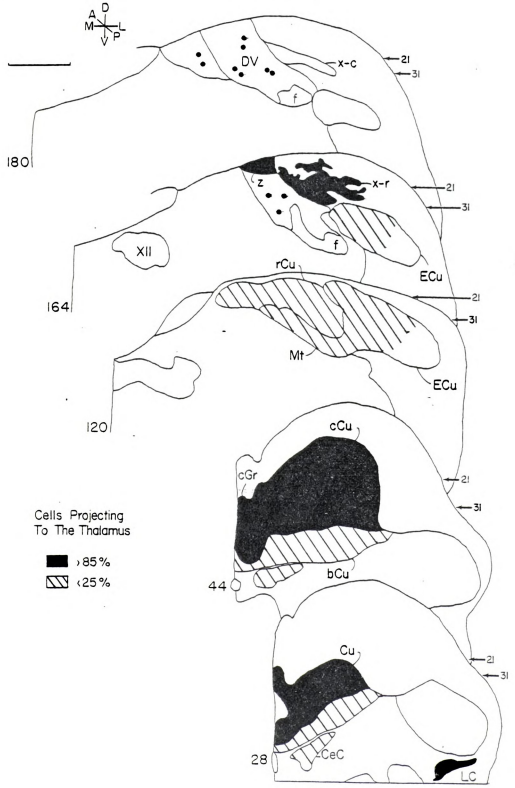
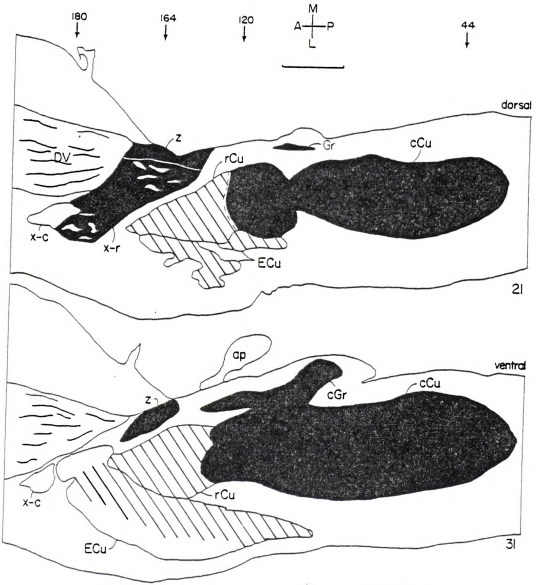

A
D
M
L
V
P
DV
x-c
2I
3I
f
180
z
x-r
2I
3I
XII
f
rCu
ECu
164
2I
3I
Mt
ECu
120
cCu
cGr
2I
3I
Cells Projecting
To The Thalamus
>85%
<25%
44
bCu
Cu
2I
3I
28
xCeC
LC

Figure 1.5 Medullary cell labeling following large thalamic HRP injections shown in the horizontal plane.

Shown here are two horizontal sections through the dorsal medulla of animal 597 (see Figure 1.3 A for injection site). The distinction between cg x-c and x-r (see also Figure 1.6) as well as that between the rCu and cCu (see Figure 1.7) may be seen in horizontal sections. The relative numbers of labeled cells are indicated as in Figure 1.4. Numbered arrows across the top indicate the level of the transverse sections shown in Figure 1.4. Bar equals 1 mm.

Figure 1.5


180
164
120
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44
dorsal
z
DV
rCu
Gr
cCu
x-c
x-r
ECu
2l
ventral
ap
z
cGr
cCu
x-c
rCu
ECu
3l
Cells Projecting To The Thalamus
> 85%
< 25%

Figure 1.6 Photomicrographs showing the distinction between the cg x-c and x-r in the horizontal plane.

A. This is a horizontal section through the cg x from an animal receiving a thalamic injection (597). Rostral is to the left, and lateral is down. In this section portions of the cCu, rCu, ECu, cg x-r and x-c may be seen. Cells in the cg x-r are labeled following thalamic injections while those in the cg x-c are not. Bar equals 1 mm. This is better seen at higher magnification. B. Higher magnification of the area outlined in the line drawing A' containing portions of both the cg x-c and x-r. Many cells in the x-r are labeled while those in the x-c do not show label. This section was reacted with TMB and neutral red counterstained. Bar equals 100 μm.

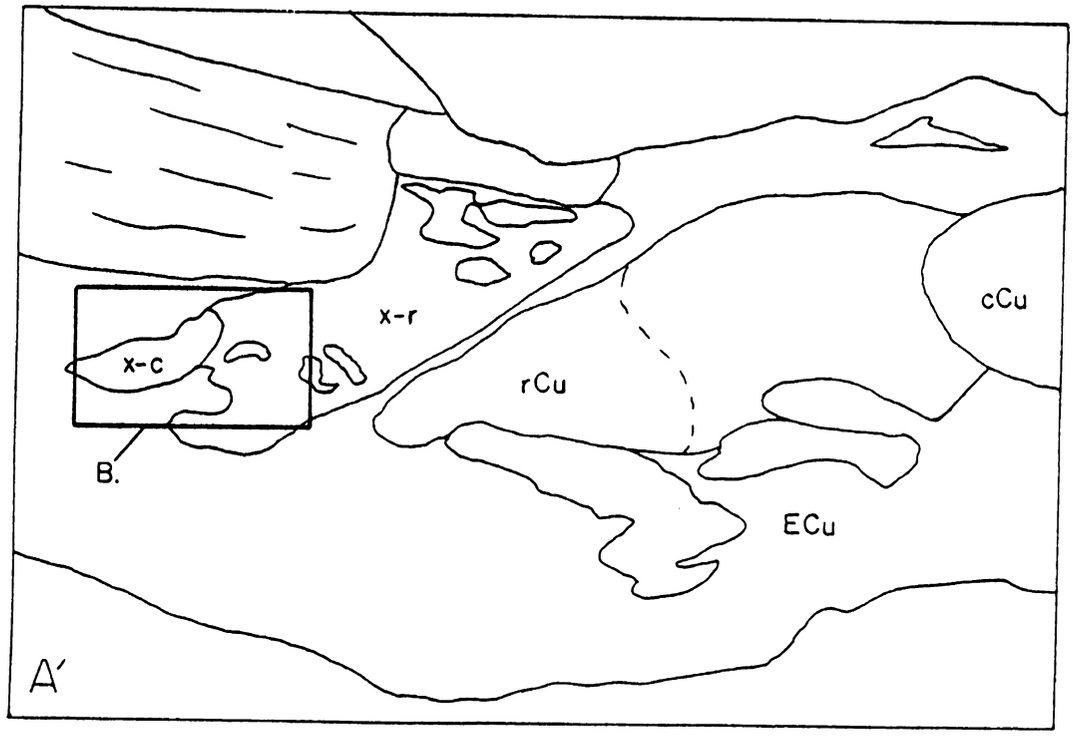
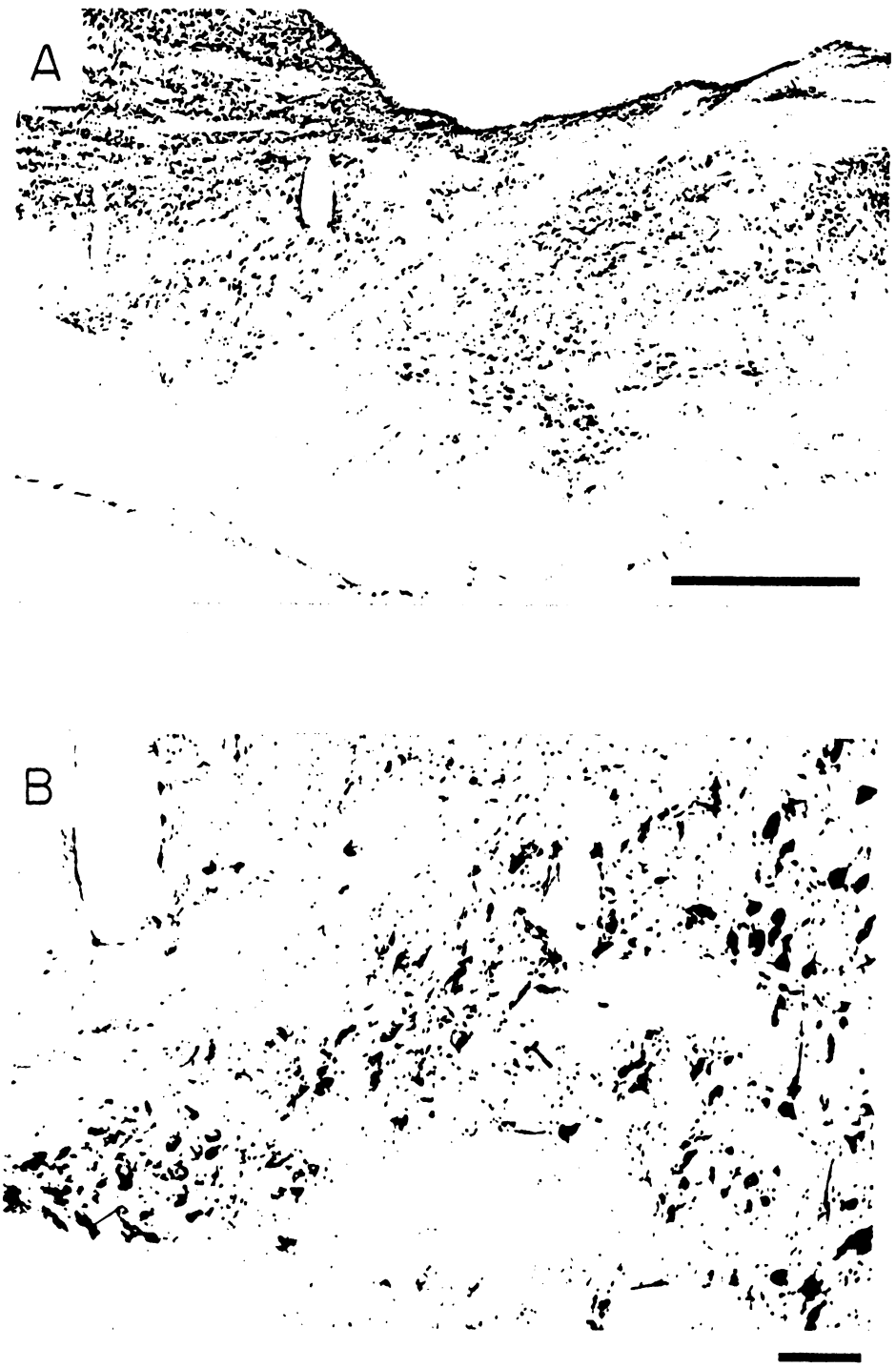


Figure 1.6



label (Figure 1.7 A-C).

Bilateral Medullothalamic Projections

In three cases (506, 586 and 597) very large complete filling of one side of the thalamus with HRP resulted in a very small number of labeled cells in the DCN on the side ipsilateral to the injection. These cells were found in the cluster region most often inbetween, not within the clusters or in the region near the border between the cuneate and gracile nuclei. Rostrally, in the cg z ipsilateral to the injection a very few HRP positive cells in the same cases were observed. We do not believe that these labeled cells were the result of HRP spread across the midline of the thalamus as in these cases the injection sites were clearly confined to one side.

Other Sources of Medullothalamic Projections

Within the rostrocaudal extent of the medulla examined in these studies, labeled neurons were observed following large thalamic injections in other nuclei as well as those in the dorsal mechanosensory medulla. Caudally these included the lateral cervical nucleus. Very heavy filling of nearly all the cells in the upper two cervical levels (only those levels were included in our tissue blocks) was observed. The Central Cervical nucleus also showed some scattered cell filling at these levels.

Rostrally, we observed substantial numbers of filled cells in a cell group associated with the lateral reticular nucleus called the infratrigeminal nucleus (IFT) by Berman ('68). We also observed a few scattered labeled cells in the descending and medial vestibular nuclei.

Figure 1.7 Photomicrograph of horizontal sections showing cell labeling in the ECu after thalamic injection of HRP.

A, A'. This is a section through the center of the ECu from the same animal as in Figure 1.6, approximately 600 μm ventral to show the location of some of the labeled cells in the ECu following thalamic injections. Figures 1.7 B,C are higher magnifications of labeled cells in the ECu at the locations indicated in A',below. Bar equals 1 mm. B. Two heavily labeled cells (arrow) and one lightly (double arrow) cell near the caudal pole of the ECu are shown here. C. Two heavily labeled cells (arrows), located more medially but still within the ECu, following large thalamic injections. B, C. Bar equals 50 μm.

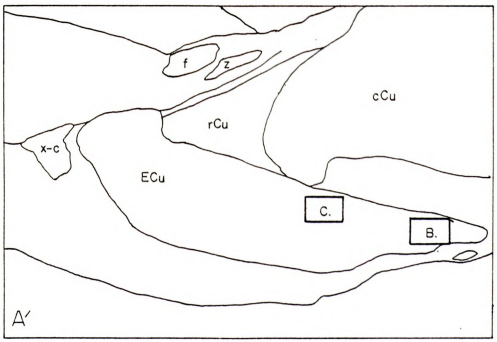
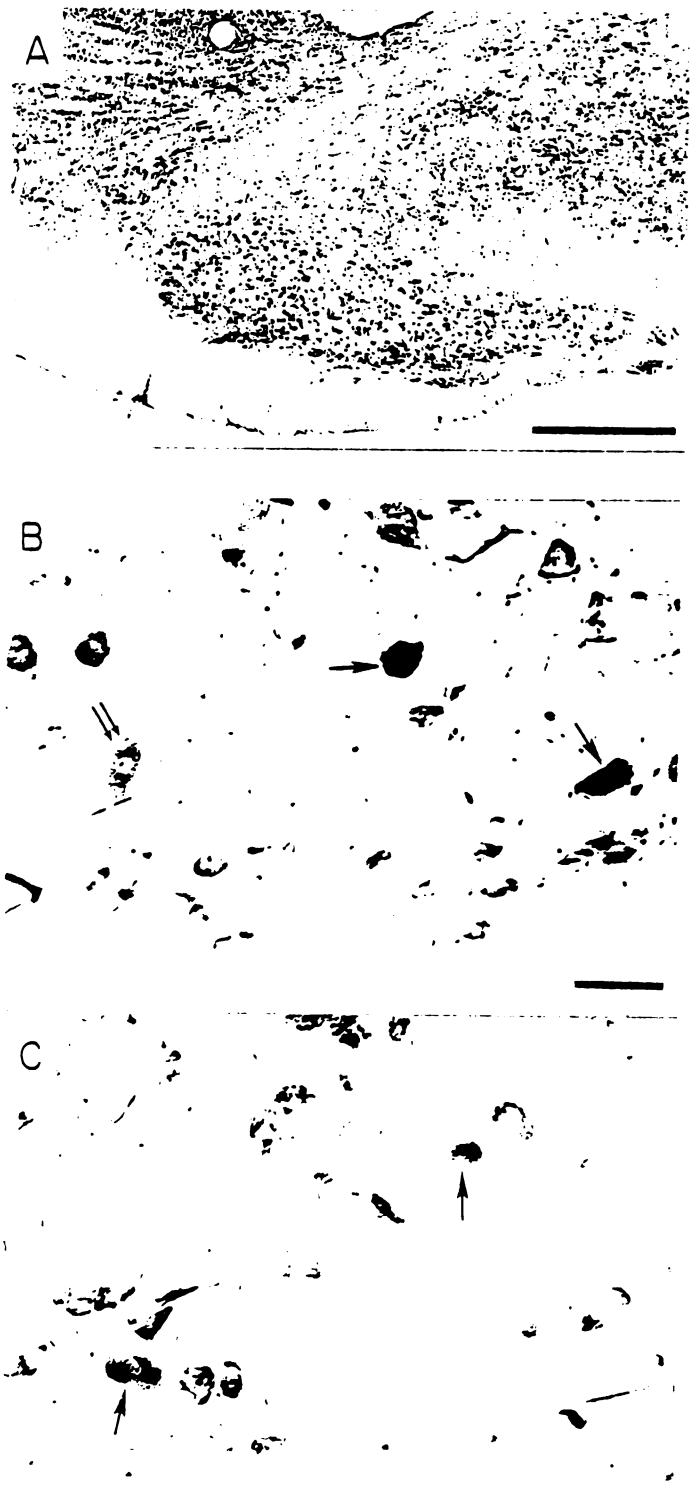


Figure 1.7



Medullocerebellar Projections

The regions of the cerebellar cortex injected with HRP in these studies (Figure 1.8) were those reported in the cat to receive somatosensory projections (Cooke, Larson, Oscarsson & Sjolund '71 a, b). Hence the majority of label observed was located in the mechanosensory medulla. Again two patterns in the proportion of labeled versus unlabeled cells were observed, in these areas ipsilateral to the injection site (Figures 1.9, 1.10). The cells in the ECu, long known as a primary source of mechanosensory projections to the cerebellar cortex were observed to be virtually all filled with dense accumulations of HRP reaction product. The Mt extension of the ECu lying beneath the rCu was also very heavily labeled as was (Figure 1.11) a cell group in the caudoventral descending vestibular nucleus resembling that called cg f by Brodal & Pompieano ('57a).

Fewer labeled cells (approximately 50%), though these were no less densely labeled, were observed in cg x-c. A small group of labeled cells in the cCu, near the caudal pole of the ECu were also observed. These were situated at the extreme lateral edge of the Cu, outside of the central cell clusters. Some scattered labeled cells were also observed in the external polymorphous ring surrounding the cell clusters, and in the rCu.

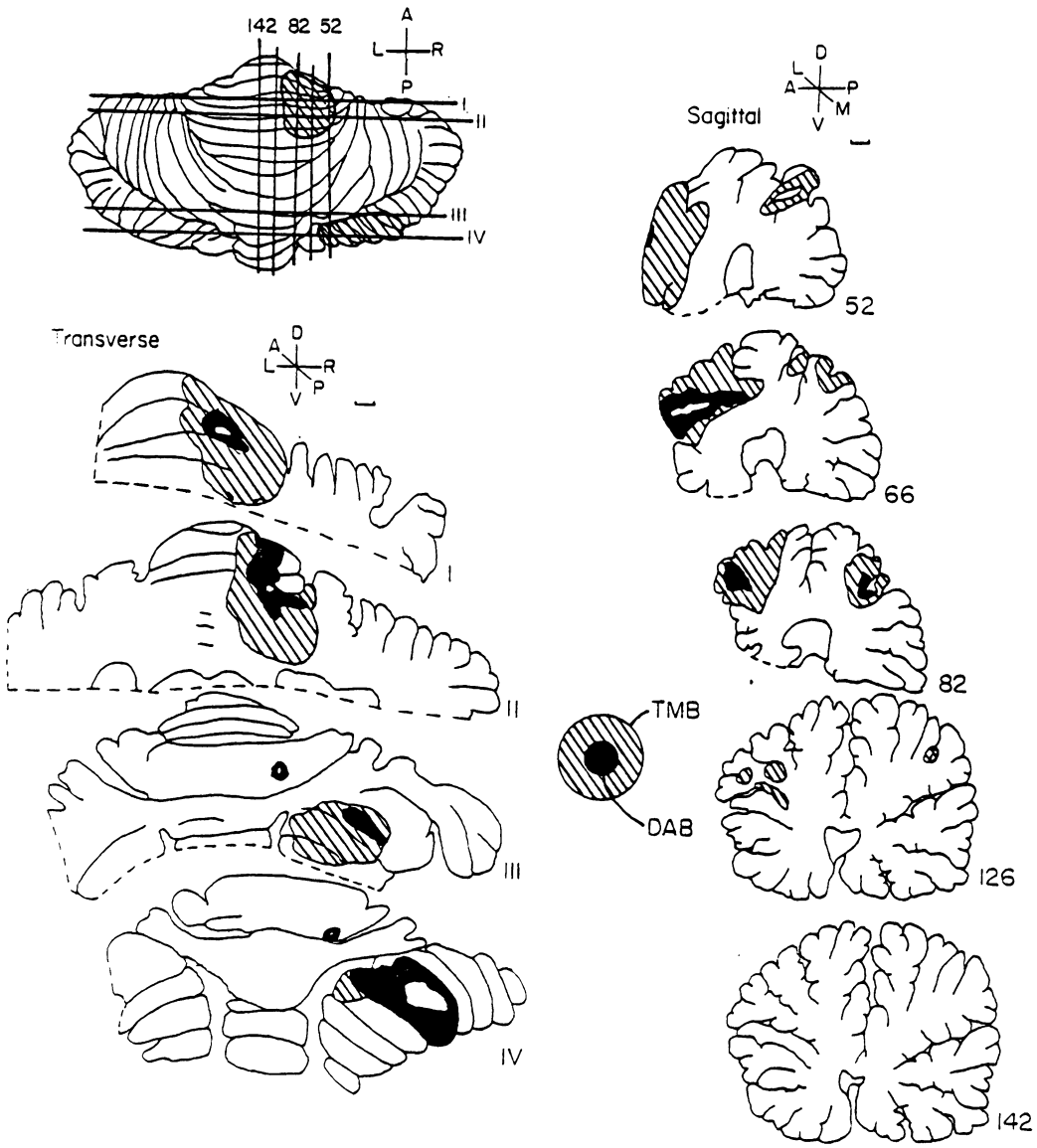
Bilateral Medullocerebellar Projections

In all the above cell groups (ECu, Mt, cg x and f, and the Cu group) labeled cells were observed on the side contralateral to the injection site, though with differing proportions of labeled cells and

Figure 1.8 Reconstructions of large cerebellar injections

Two of the large cerebellar injections used in this study are shown here in series of transverse (animal 513, left) and sagittal (591, right) sections. The approximate location of these sections are shown in the diagram of the dorsal cerebellar surface in the upper left. See Figures 1.9 and 1.10 for the distribution of labeled cells in each case. The injection sites in this figure are indicated both for TMB (diagonal stripe) and DAB (solid black) from adjacent sections. Note that the anterior injection sites do not extend to the midline of the vermis even in the TMB reacted sections. This was true for all the animals used in this group. Bar equals 1 mm.

Figure 1.8


142 82 52
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Transverse
D
A
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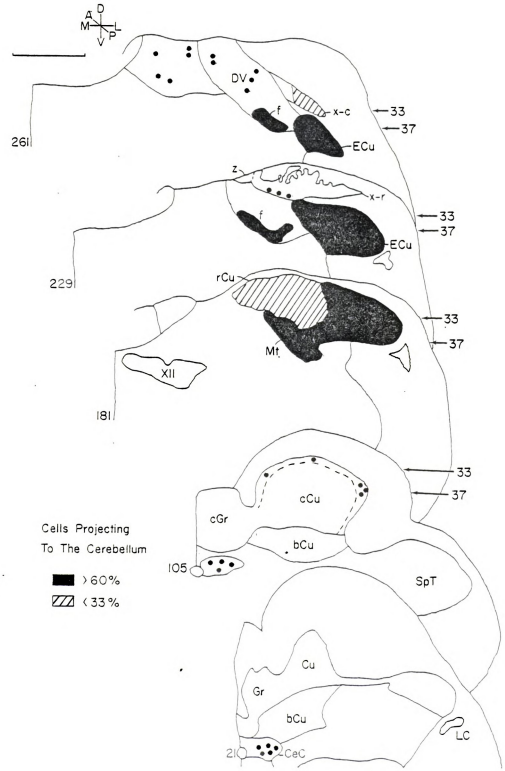
III
IV
Sagittal
D
L
A
P
M
V
52
66
82
TMB
DAB
126
142

Figure 1.9 Cell labeling in the dorsal mechanosensory medulla following large cerebellar injections.

This figure shows a series of transverse sections through the dorsal medulla of animal 513. Areas in which 60-75% of the cells in these sections were labeled are indicated in black. These include the ECu and the Mt. The right diagonal shading indicates areas in which 17-33% of the cells were labeled. These include the rCu and cg x-c. In the rCu most of the largest cells in the subdivision were labeled, some smaller cells were also labeled. In the cg x-c the majority of labeled cells were in the lateral one-third of the cell group (in this one-third approximately half of the cells were labeled). Areas with only a few labeled cells are indicated by the dots. These included the vestibular nuclei, the polymorphous ring surrounding the dorsal and lateral edge of the cCu and the base of the cg x-r. These latter cels were found exclusively at the ventral boundary of the cg x-r where it borders on the descending vestibular nucleus and not in the cells strands lying more dorsally. The approximate level of these section is shown by the numbered arrows in Figure 1.10. Bar equals 1 mm.

Figure 1.9


A
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DV
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33
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ECu
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x-r
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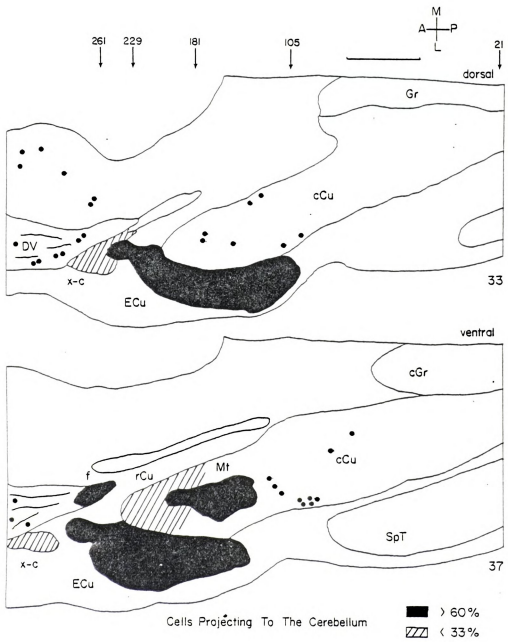
37
f
ECu
229
rCu
33
37
Mt
XII
181
33
37
cCu
cGr
bCu
105
SpT
Cu
Gr
bCu
LC
21
CeC
Cells Projecting
To The Cerebellum
>60%
<33%

Figure 1.10 Distribution of labeled cells in horizontal sections through the dorsal medulla following cerebellar injections.

This figure show the distribution of labeled cells following cerebellar injections in animal 591 (see Figure 1.8 B for the injection sites). The frequencies of labeled cells in the nuclear subdivisions are indicated as in Figure 1.9 except in this case almost 80% of the cells in the ECu were labeled: black 60-80%; diagonal shading 17-33%; dots less than 17% of cells labeled. ECu-Mt nuclear areas showed the highest frequency of labeled cells while the cg x-c and rCu were intermediate and the vestibular nuclei and polymorphous ring around the cCu showed a few scattered labeled cells. The approximate level of these sections is shown by the numbered arrows in Figure 1.9. Bar equals 1 mm.

Figure 1.10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ventral
cGr
cCu
f
rCu
Mt
SpT
x-c
ECu
37
Cells Projecting To The Cerebellum
> 60%
< 33%

Figure 1.11 Horizontal section illustrating the cellular bridge connecting the ECu and Mt.

This is a horizontal section intermediate between those shown in Figure 1.10 from the same animal illustrating both the cerebellar projections of the cells in the ECu (laterally) and Mt (medially) as well as the cellular bridge connecting the two nuclear regions. This section was reacted with TMB and neutral red counterstained. Bar equals 1 mm.

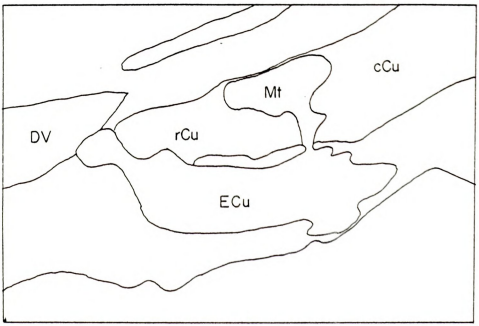
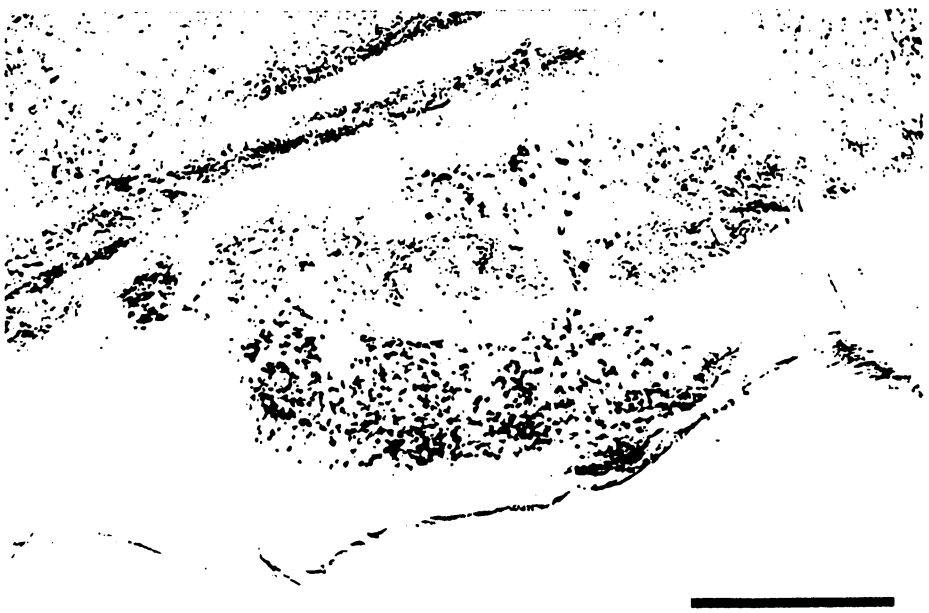


Figure 1.11



density of cell labeling. A more detailed consideration of the bilateral distribution of these projections has been presented elsewhere (Ostapoff '82, Ostapoff & Johnson '83a).

Other Medullocerebellar Projections

Following these injections into the cerebellar cortex labeled cells were observed in the lateral reticular nucleus of both sides, with the ipsilateral side showing more labeled cells. The inferior olive contralateral to the injection site was also heavily labeled. The descending and medial vestibular nuclei and the central cervical nucleus (the latter bilaterally) had a few scattered labeled cells in our material.

DISCUSSION

Cuneate Nuclear Projections to Thalamus

The dual nature of the labeling observed in these experiments further justifies the parcellation of the major nuclei in the dorsal mechanosensory medulla into several subregions. The heavy labeling in the cluster region of the cuneate and gracile nuclei (cCu) (including the external polymorphous ring), long considered the primary thalamic projecting areas (Lund & Webster '67, Cheek, Rustioni & Trevino '75, Hand & van Winkle '77) is starkly contrasted by the relatively sparse labeling in the two other subregions of the CuGr considered here (i.e. the rCu and bCu). The rCu in the cat has been reported to project to a wide variety of non-thalamic targets (other brainstem nuclei, Berkley '75, Hand & van Winkle '77; tectum, Berkley & Hand '78, Robards '79;

spinal cord, Burton & Loewy '77). Considering the relatively few cells in this region labeled by very large thalamic injections of HRP, it would not be surprising if a similar heterogenous set of projections to non-thalamic targets from the rCu was present in the raccoon.

The bCu has been reported to receive, in addition to dorsal column projections, a cortical input (Kuypers & Tuerk '64, Weisberg & Rustioni '79), and a dorsolateral funiculus input (Rustioni & Kaufmann '77, Rustioni & Molenaar '75, Miller & Basbaum '76). Projections from the bCu to the spinal cord and lateral cervical nucleus have been described (Burton & Loewy '77, Craig '78). It is clear from the data presented here that only a few cells in these two regions of the Cu project to the thalamus in the raccoon. A more precise localization of the terminal field of the bCu projections to the thalamus in the raccoon is presented elsewhere (Ostapoff & Johnson '83a).

External Cuneothalamic Projections

A projection to thalamus from the ECu has not been previously reported in carnivores. However such a projection has been recently reported in monkeys by Boivie and coworkers (Bovie, Grant, Albe-Fessard & Levante '75, Boivie & Bowman '81). The projection reported here for the raccoon appears to be somewhat more sparse (i.e. fewer cells were labeled) than that reported for monkey (Boivie et al '75). Whether or not, as Boivie and Bowman ('81) suggest,this pathway represents a phylogenetically recent development, its presence in the monkey and raccoon and reportedly not in the cat would suggest a relationship of this pathway to the forepaw manipulative behaviors exhibited by the two former species.

Cell Group z and x Thalamic Projections

These present studies confirm that in the raccoon most of the cells in cg z project to the thalamus as reported in the cat (Grant, Boivie & Silfvenius '73). The present experiments demonstrate that most of the cells in the cg x-r also project to the thalamus agrees in part with a report that some (2 of 8 reported) cells in an apparently similar location receiving hindlimb muscle afferent projections could be antidromically activated from the thalamus (Johansson & Silfvenius '77a, b).

Medullary Projections to Cerebellar Cortex

The association of the Mt region with the ECu in the raccoon is supported by the obvious heavy labeling of the majority of cells in the ECu, Mt and cells connecting the two, following injection of HRP into the somatosensory areas of the cerebellar cortex (Figures 1.9, 1.10). relative sparcity of labeled cells in the rest of the rCu in raccoon This contrasts somewhat with reports in the cat (Cooke et al. '71a). These authors found that cerebellar relay cells activated by cutaneous afferents were intermingled with lemniscal neurons. This lack of mingling of cerebellar projecting and thalamic projecting neurons in the raccoon rCu has been previously reported (Haring '81). In the latter report the majority of cells rostral to the obex, not in the ECu, projecting to the cerebellum were located in the Mt. A few cells in the polymorphous ring surrounding the cCu projecting to the cerebellar cortex in raccoon as described here have also been reported (Warren, Rowinski, Maliniak, Haring & Pubols '80).

Approximately one-third of the cells in the cg x-c in this study projected to the areas of the cerebellar cortex injected with HRP. None of the cells in the dorsal strings of cells of cg x were labeled following these injections, though some few of the cells along the border between the cg x-c and the descending vestibular nucleus were labeled. In the cat some cg x cells were reported to project to the somatosensory areas of the cerebellar cortex (Johansson & Silfvenius '77a, b) while Brodal & Pompeiano ('57a) describe a projection from cg x to the vestibular portions of the cerebellar cortex. We did not investigate this latter projection but the projection from cg x-c to our cerebellar injection sites was approximately equal bilaterally.

Cell Groups x and z as a Complex. Despite the "clear distinction" of cg x from cg z in the cat (Brodal & Pompeiano '57a, p. 446), in the raccoon we view these cell groups as forming a continuous band, caudomedial to rostrolateral, separating the nuclei of the dorsal columns (CuGr, ECu) from those of the vestibular complex (DV, MV). This region might therefore better be designated as a complex (the xz complex) much as we do for the cuneate and gracile nuclei. Segregation of the cg z from the cg x has also been made on the basis efferent projections. In cats, cg z has been shown to project to the thalamus (Landgren & Silfvenius '70,'71) while cg x projects to various areas of the cerebellar cortex (Brodal '81). The present study also shows that in raccoon, cg x-r, in addition to cg z projects heavily to the thalamus while cg x-c projects, in part, to the somatosensory areas of the cerebellar cortex (see also Ostapoff & Johnson '83a). The subdivision here called cg x-r projects, parallel to cg z, to the

thalamus but clearly lies within the regions shown as cg x in the cat (Brodal & Pompeiano '57a, text-figure 3; Johansson & Silfvenius 77c, text-figure 2, c.f. our Figures 1.4-1.6). A better designation for the cg x-r might be the intermediate reticular portion of the xz complex (cg xz-r). A more detailed consideration of this region is currently in preparation (Ostapoff & Johnson '83d).

Nuclear Subregions Projecting to Both the Thalamus and Cerebellar Cortex

Figure 1.12 shows a summary of the distribution and relative density of labeled cells following either cerebellar of thalamic injections. Three of the nuclear subregions identified in this study appear to contain subpopulations of cells which label following both large thalamic and large cerebellar injections.

Rostral Cuneate. The polymorphic rCu is one of these subregions. In our cell counts approximately equal numbers of cells were labeled following both cerebellar injection (17%) and thalamic injection (20%).

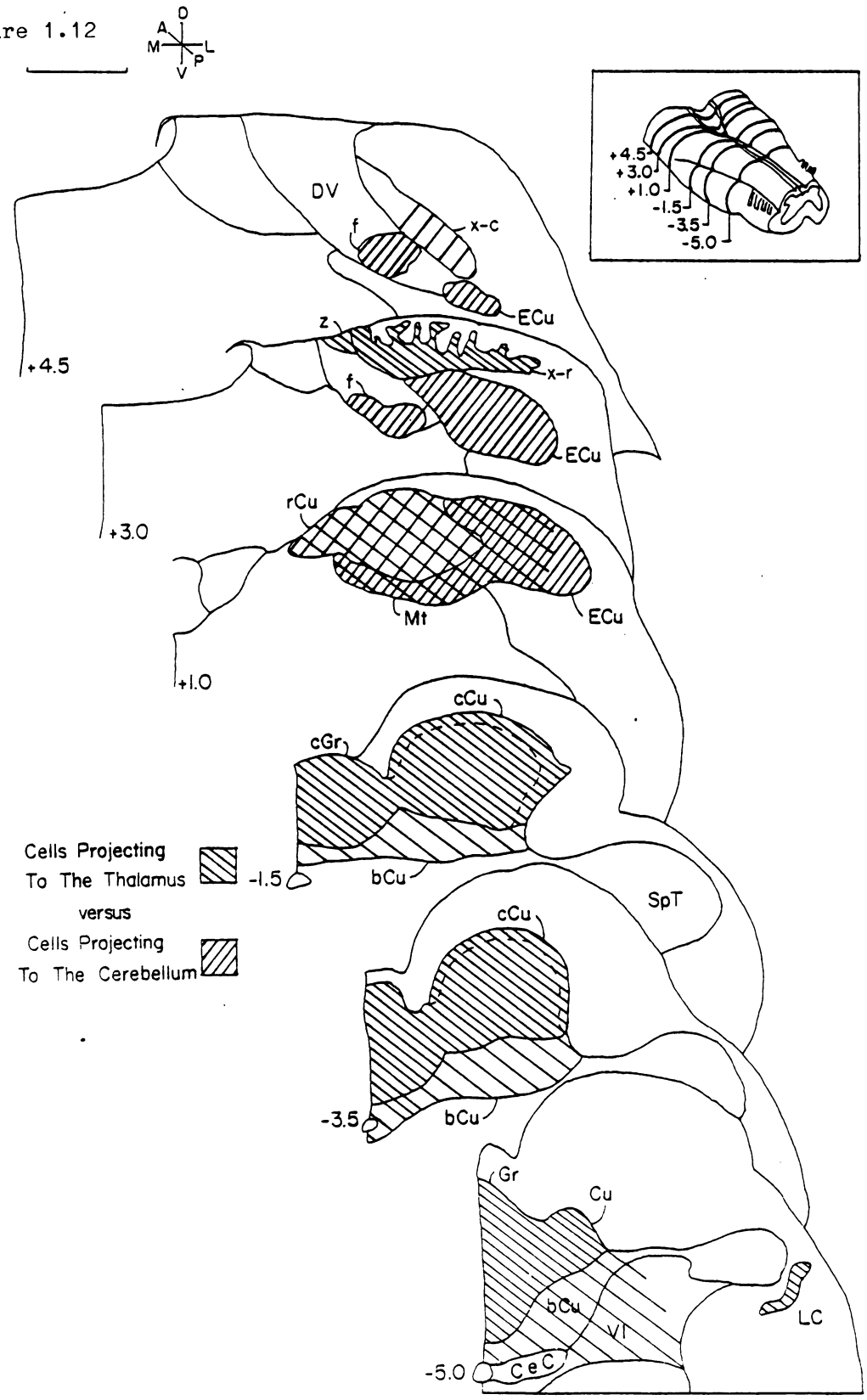
External Cuneate and Medial Tongue. The ECu and Mt also contain labeled cells following both cerebellar and thalamic injections. In this case however, the majority of cells in the ECu (greater than 70%) and Mt (greater than 60%) project to the cerebellar cortex while smaller numbers of cells in these subregions (9 and 21% respectively) project to the thalamus (Ostapoff & Johnson '83c).

The few cells in the polymorphic ring surrounding the cCu and projecting to the cerebellar cortex are similarly scattered among the majority of cells projecting to the thalamus.

Figure 1.12 Summary of cerebellar projecting versus thalamic projecting cells in the dorsal mechanosensory medulla.

This figure shows a series of drawings of transverse sections through the raccoon medulla. Left diagonal shading indicates areas in which cells project to the thalamus. Closely spaced diagonal lines indicate that the majority of the cells were labeled. These areas include the cg x-r and the cluster region of the CuGr. Widely spaced lines indicate that a minority of the cells in those areas project to the thalamus. These areas include the ECu (9%), Mt (21%), rCu (20%) and bCu (26%). Right diagonal shading indicates areas in which cells were labeled after our cerebellar injections. Closely spaced diagonal lines indicate areas in which at least 62% of the cells were labeled. The areas included the ECu (70%) and the Mt (62%). Widely spaced diagonal lines indicate areas in which fewer cells were labeled from our cerebellar injections. These areas include the cg x-c (33%) and the rCu (17%). Three nuclear subregions stand out as containing cells which label following both cerebellar and thalamic injections. These are the rCu, in which aproximately equal numbers of cells project to each target and the ECu-Mt in which the majority of cells project to the cerebellar cortex but a sizeable minority project to the thalamus (9% of the cells in the ECu and 21% of the cells in the Mt). Bar equals 1 mm.

Figure 1.12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z
x-r
f
ECu
+4.5
rCu
+3.0
Mt
ECu
+1.0
cCu
cGr
Cells Projecting
To The Thalamus
versus
Cells Projecting
To The Cerebellum
-1.5
bCu
SpT
cCu
-3.5
bCu
Gr
Cu
bCu
VI
LC
-5.0
CeC

It is logically possible that some of these cells project to both the thalamus and the cerebellar cortex. Two studies designed to address this question have failed to demonstrate either anatomically (cat, Rustioni, Hayes & O'Neill '79) or physiologically (raccoon, Haring '81) that there are cells sending axon collaterals to both the cerebellar cortex and thalamus. What may rather be the case is that some cells in regions projecting primarily to the cerebellar cortex may be sending a sample of this information to the thalamus (and presumably from there to the cerebral cortex; and vice versa, a sample of thalamically directed information similarly arrives in cerebellar cortex. The cg x is thought to be innervated by axon collaterals from the dorsal spinocerebellar tract in cats (Johansson & Silfvenius '77a). If this is case in raccoons, then functionally the cells in the cg x-r may serve an analagous sampling function for the information being conveyed by the tract. An analagous situation may exist in other subregions of the DCN known to project to non-thalamic targets. That is, those cells in the bCu and rCu projecting to the thalamus may represent the means by which cerebral cortex is informed about the integration of activity taking place at the medullary level and projected to non-thalamic targets.

CHAPTER III. DORSAL MEDULLARY SOURCES OF PROJECTIONS TO THE KINESTHETIC THALAMUS

INTRODUCTION

Evoked responses from stimulation of the deep tissues of the body can be recorded in the transitional cortex (area 3a) between the classical motor (area 4) and somatosensory (area 3b) cerebral cortices in monkeys (Phillips, Powell & Wiesendanger '71; Tanji & Wise '81; Wise & Tanji '81; Merzenich, Kaas, Sur & Lin '78), cat (Kaas, Nelson, Sur, Lin & Merzenich '79) and raccoon (Johnson, Ostapoff & Warach '82). A similar kinesthetic zone or shell has recently been described physiologically in the monkey thalamus (Dykes, Sur, Merzenich, Kaas & Nelson '81; Maendley, Ruegg, Wiesendanger, Wiesendanger, Lagowsky & Hess '81), and raccoon (Wiener, Johnson & Ostapoff '82). Reciprocal thalamocortical projections of this kinesthetic shell in the thalamus with area 3a cortex in the monkey have also been shown (Jones & Friedman '82; Jones, Friedman & Hendry '82).

Little is known of the sources of these kinesthetic projections to the thalamus. Physiological studies using both natural and electrical stimulation of nerves presumed to carry muscle afferent fibers have reported several nuclear regions in the dorsal medulla that respond to kinesthetic stimulation. These include the caudoventral (or basal) Cuneate and Gracile nuclei (cat: Dykes, Rasmusson, Stretavan & Rehman '82; tree squirrel: Ostapoff, Johnson & Albright, in press); the ventral portion of the rostral Cuneate nucleus (cat: Dykes et al. '82; Rosen '69a,b, Rosen & Sjolund '73a,b; Rosen & Asanuma '73; raccoon: Johnson, Welker & Pubols '68); the External Cuneate nucleus (cats:

Cooke, Oscarsson & Sjolund 71a,b; Dykes et al. '82; raccoons: Johnson et al. '68; tree squirrel: Ostapoff et al., in press) and cell groups z and x (Landgren & Silfvenius '69, '70, '71).

Anatomical demonstration that any of these nuclear regions responding to kinesthetic stimulation project to the kinesthetic thalamus is somewhat limited. Grant, Boivie & Silfvenius ('73) using the Fink-Heimer technique, following lesions in the dorsal medulla (only one of which was confined to cell group z) reported that projections from this area of the dorsal medulla terminated in the caudolateral part of the ventrolateral nucleus (VL), immediately adjacent to the rostral dorsolateral part of the ventrobasal complex (VB). In a more recent article, Hendry, Jones & Graham ('79) showed that the caudal part of the VL does not receive deep cerebellar input nor does it project to area 4 of the cortex. This region was also identified as analagous to that region receiving spino- and cervicothalamic input by another author (Boivie '70, '71a) and not to include regions of VB to which the gracile nucleus (Boivie '71b) and the cervicothalamic fibers (Boivie '78) project.

A pathway from the ventral portion of the rostral Cuneate nucleus via the thalamus by which forelimb kinesthetic information may reach the cerebral cortex of cat was described by Oscarsson and Rosen ('63).

Recently Boivie and coworkers described an External Cuneothalamic pathway in the monkey (Boivie, Grant, Albe-Fessard & Levant '75, Bovie & Bowman '81).

Recent work in our laboratory (Wiener et al. '82) has shown that the raccoon VB has a large kinesthetic region as compared with the monkey (Dykes et al. '81, Maendley et al. '81, Jones & Friedman '82,

Cooke, Oscarsson & Sjolund 71a,b; Dykes et al. '82; raccoons: Johnson et al. '68; tree squirrel: Ostapoff et al., in press) and cell groups z and x (Landgren & Silfvenius '69, '70, '71).

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Recent work in our laboratory (Wiener et al. '82) has shown that the raccoon VB has a large kinesthetic region as compared with the monkey (Dykes et al. '81, Maendley et al. '81, Jones & Friedman '82,

Jones et al. '82). In this region we made small injections of horseradish peroxidase (HRP), closely guided by simultaneous physiological recording of evoked responses to peripheral stimulation, to determine the medullary sources of the kinesthetic projections.

METHODS

Nine raccoons were used for this series of experiments. Surgical and histological procedures were as previously described (Ostapoff & Johnson '83b). In each animal a grid of standard tungsten microelectrode penetrations (Johnson, Ostapoff & Wwarach '82) was made in the rostral third of the ventrobasal complex, specifically locating the kinesthetic region (KVB) with respect to the underlying cutanous projections. All injections reported in this study were made while simultaneously recording evoked potentials to peripheral stimulation of the forelimb. Target sites in the KVB fulfilled the following criterion with respect to modality of effective stimulation. The responses at the injection site could be elicited only by stimulation of the deep tissues of the forelimb. Deep tissue was defined in two ways: 1) either joint movement or visibly large indentation of the tissues was necessary to evoke maximal responses and 2) in areas of the body covered by loose skin (e.g. upper arm) the receptive field must have remained fixed with respect to the deep tissues as the superficial skin was displaced. The recording microelectrode was then replaced by an HRP filled glass pipette with a tip inner diameter of 50 to 80 um into which a moveable tungsten filament (diameter 30-70 um) was inserted so that 20-40 um of tungsten extended beyond the glass tip. This was then lowered into the KVB until evoked responses to

kinesthetic stimulation of the forelimb were recorded through the exposed tungsten tip. The tungsten was then retracted, allowing the HRP to be drawn by capillary action to the glass tip. This HRP was then expressed by re-extending the tungsten. At this time the receptive field could be re-examined to ensure against inadvertant electrode movement. The size of the injection site could to some extent be controlled by: varying the the amount of time allowed for HRP filling of the tip and the number and frequency of tungsten withdrawal/extension cycles made. The injections were targeted to lie in either the medial or lateral halves of the KVB as determined by the underlying cutaneous representation (lateral half overlying the representation of digits 4 and 5, medial half overlying projections from digits 1, 2 or 3). In most cases the relationship between these kinesthetic responses to the underlying cutaneous projections was known either by advancing the injecting electrode into the cutaneous projections before injecting the HRP at more dorsal levels or by subsequent histological reconstruction of the pre-injection mapping penetrations. This allowed us to place the kinesthetic projections within the organizational and stereotaxic framework developed by us in a separate fine grain mapping study of the organization of projections in the KVB (Wiener et al '82)

Following a survival time of 3-4 days, all animals except those selected for post-injection mapping of their medullas (see below), were perfused and their brains treated for routine HRP visualization as in previous studies (Ostapoff & Johnson '83b).

All the sections through the dorsal medulla were systematically examined for labelled cells at a magnification of 125X and

reconstructions of the location of all labeled cells in every fourth section through the dorsal medulla were made with the aid of a drawing tube attached to a Zeiss microscope at a magnification of 50X. These were then fitted onto a standardized series of drawings of the raccoon dorsal medulla at six representative levels to facilitate comparisons. Previous studies in the raccoon have identified six sub-regions of the nuclei in the dorsal medulla other than the cluster region of the CuGr projecting to the thalamus (Ostapoff & Johnson '82b). These include the base of the cuneate nucleus (bCu), the heterogenous portion of the rostral Cuneate (rCu), the External Cuneate nucleus (ECu) and its medial tongue (Mt), and cell groups z (cg z) and x (cg x). In addition cell group x was further subdivided into a reticular portion (cg x-r) projecting to the thalamus and a compact portion (cg x-c) projecting in part to the cerebellar cortex (Ostapoff & Johnson '83b).

Physiological Mapping of the Medulla

The mapping data for the primary afferent projections to nuclei in the medulla of the raccoon (Johnson et al. '68) extensively describe projections to the Cuneate, Gracile and External Cuneate nuclei but do not include data from the base of the Cuneate nucleus (bCu) nor cell groups z (cg z) and x (cg x). In order to firmly establish that these nuclear areas do indeed convey kinesthetic information, on the third or fourth survival day following HRP injection into the KVB, four animals were anesthetized as as before and surgically prepared for mapping of their medullas in the regions of the bCu and cg z and x. The medulla and caudal cerebellar vermis were exposed and rows of electrode penetrations made in the region of the bCu rostral to the spinal

cord-medullary junction, and in the region of cg z and x (approximately 1 to 4 mm rostral to the obex and 3 to 5 mm lateral to the midline) with spacing of approximately .75 mm between penetrations. These latter penetrations were made through the overlying cerebellar cortex so as not to damage the cg z and x which lie very close to the dorsal surface of the medulla. Small microlesions were made in the vicinity of kinesthetic responses so that the actual electrode tip location could be determined. At the conclusion of the post-injection medullary mapping experiments the animals were perfused and their brains treated similarly to the rest of the subjects in this study.

RESULTS

Use of Pre-injection Thalamic Mapping to Localize Injections

The results of our fine grain mapping study of the projections to the KVB (Wiener et al. '82) were used to locate the injection sites in this study with respect to the overall patterns of projections to the VB. The physiological data as well as as the histological reconstructions of the pre-injection electrode penetrations when compared to the same data from the injecting pipette were considered in characterizing the location of the injection sites. This allows us to describe the injection sites reported here both in terms of their anatomical location and more importantly, in terms of their relationship to the observed organization of somatosensory projections to the VB complex. An example of this can be seen in Figure 2.1.

Though the kinesthetic projections to the VB are somatotopically organized, the receptor fields are quite large (presumably due to our

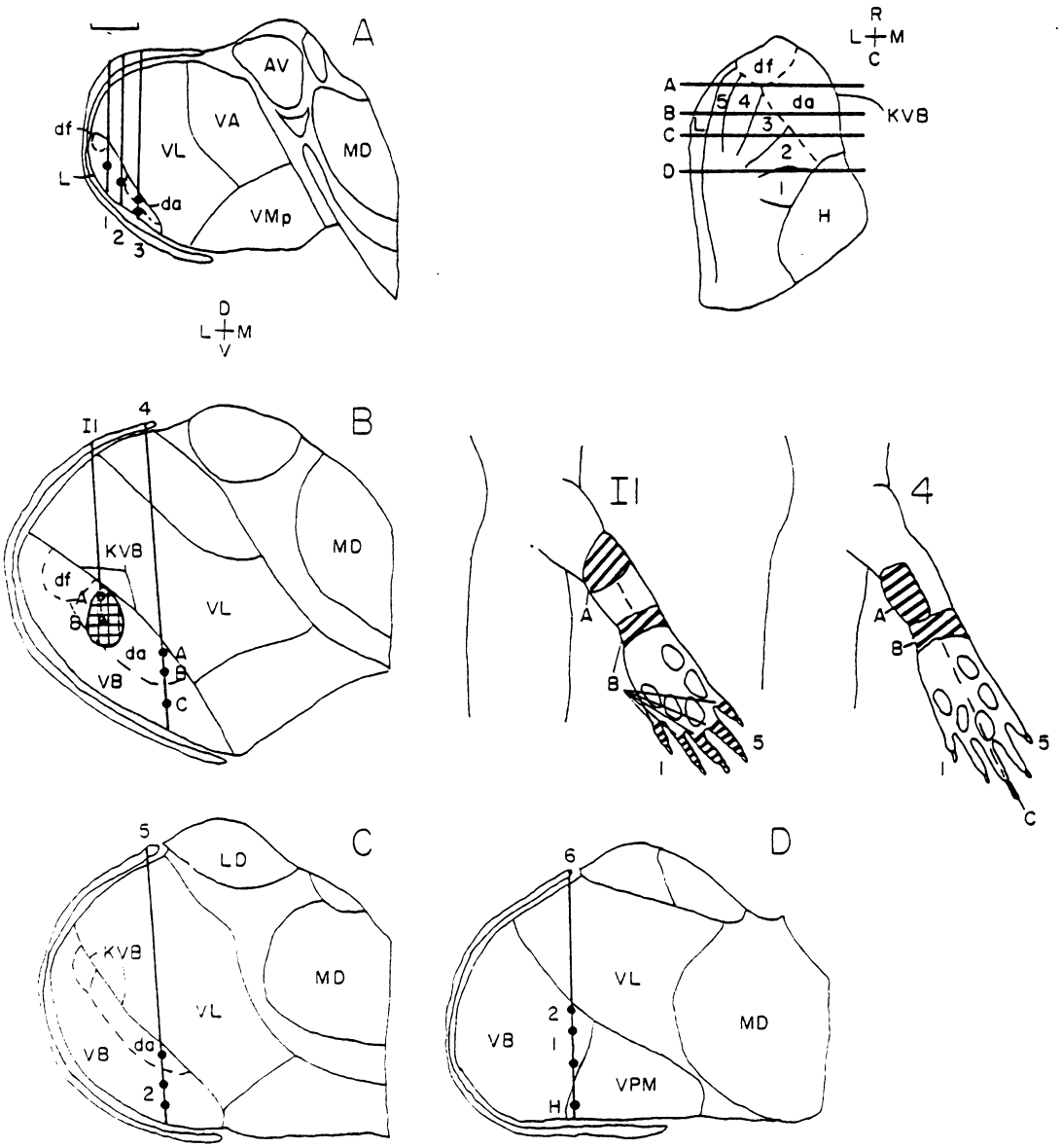
Figure 2.1 Injection into the lateral KVB.

This figure shows an example of the data used to accurately localize the injection sites in this study. At the upper right is a drawing of a horizontal section showing the approximate locations of the transverse sections drawn in A-D. This drawing is adapted from Welker and Johnson ('65, Figure 5, pp771) to show the rostral kinesthetic shell of the VB described by Wiener et al. '82). Indicated in this drawing are the representations of the cutaneous leg (L), digits of the hand (5-1), and head (H) and the (KVB) representations of the deep tissues of the leg and trunk (df) and of the arm (da) as determined by recording experiments . A-D. Line drawings of transverse sections through the VBC showing reconstructions of the pre-injection electrode penetrations (1-6) and the track of the recording/injecting pipette (I1) as well as the maximal spread of the injection site (indicated by heavy circle) for animal 533 LT. Levels A-C are separated by approximately 0.75 mm, D is 1.5 mm caudal to C. A. Responses to stimulation of the hairs covering the ankle and dorsal midline above the shoulder were recorded in penetrations 1 and 2 respectively. Penetration 3 had a locus responding to stimulation of the deep tissues of the lower forearm above a response to pad C of the hand. These responses indicate that this row of penetrations is approximately 1-1.5 mm caudal to the rostral pole of the KVB. B. The receptive fields encountered in penetration 4 and I1 are shown in the figurines to the right, center. Two loci responding to stimulation of the deep tissues of the lower arm (A and B) lay above a response to stimulation of the claw of digit 3 of the hand (C) in penetration 4. In penetration I1, the injection was made at a locus whose receptive

field was in the deep tissues of the elbow. These responses indicate that the injection was made into the lateral portion of the forelimb KVB in a zone responding best to joint movements lateral to the rostral pole of the digit 3 cutaneous representation. C. The responses recorded in penetration 5 (deep tissues of the upper arm above claw of digit 2 of the hand above the hairy dorsum of digit 2) indicate that this level passes through the rostral part of the digit 2 representation. D. Penetration 6 passed through the representations of the distal glabrous surfaces of digits 2 and 1 (upper three loci) and entered the cutaneous representation of the head in the ventroposteromedial nucleus. Regardless of which thalamus was actually injected in this and following figures, injections will be depicted as in left thalami. Likewise labeled cells in the medulla will be depicted as in right medullas. The pre-injection mapping penetrations both rostral and caudal to the injection sites in all cases were reconstructed from histological sections and used to place the injection site but only those penetrations at the same transverse level as the recording/ injecting pipette track are shown in all subsequent figures. On figurines in this and all subsequent figures, shaded areas indicate subcutaneous and black areas indicates cutaneous receptive fields. Bar equals 1 mm. E. Distribution of labeled cells following injection into the lateral KVB. Shown here is a standard series of drawings from transverse sections through the right dorsal medulla in the raccoon. Approximate levels of the transverse sections are shown in the inset at the upper left, numbers show distance from the obex in mm. Dots in this figure and all similar ones indicate the approximate location of all cells observed to contain HRP granules in every fourth

section through the contralateral dorsal medulla. In all cases this is described as the right side of the medulla. In this case the injection resulted in substantial labeling in cg x-r and z and the medial most portion of the Mt. Note the paucity of labeled cells in the ECu, lateral Mt or any of the nuclei projecting cutaneous information to the thalamus (cCuGr).

Figure 2.1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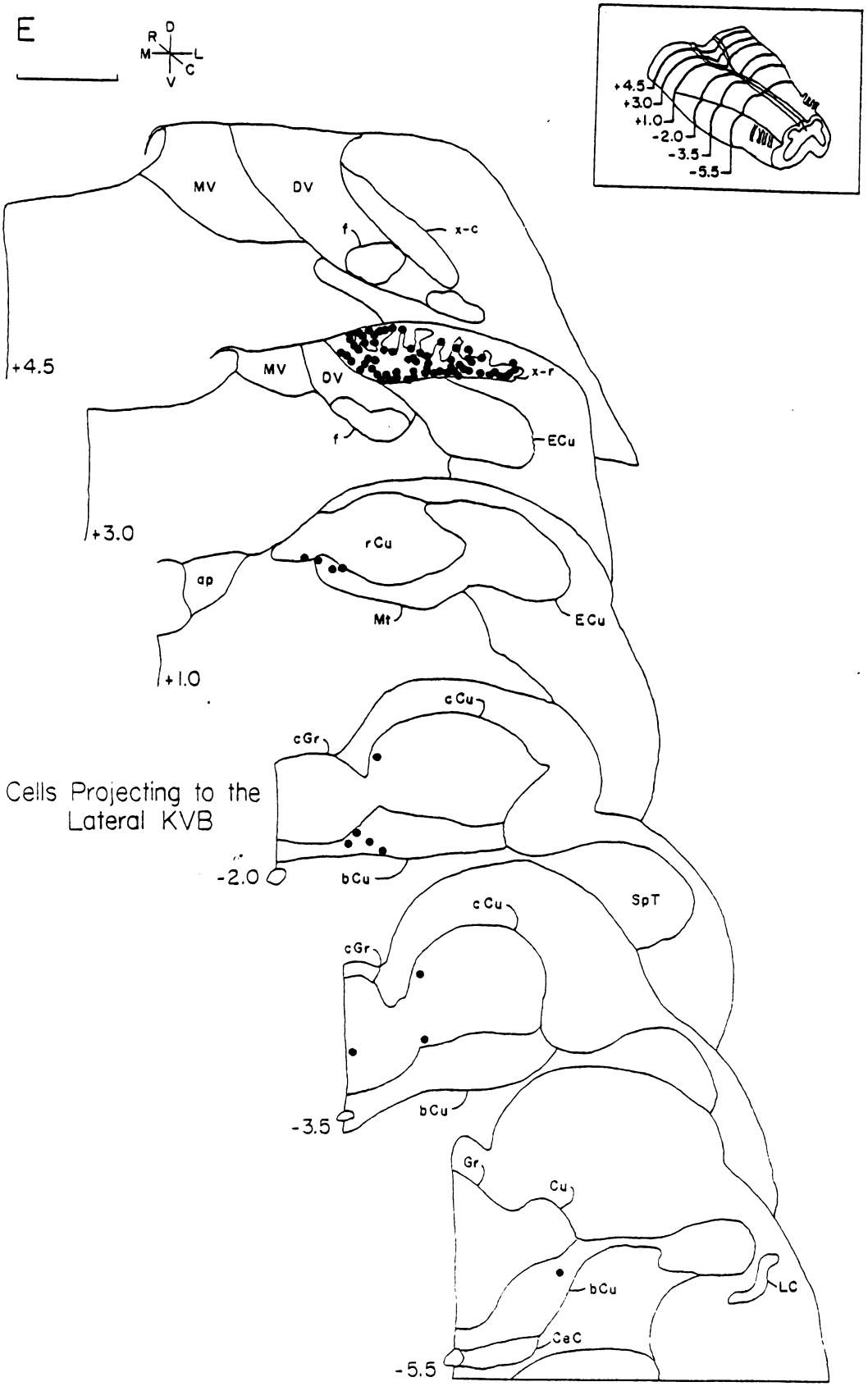
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Cells Projecting to the
Lateral KVB

stimulation techniques and connections between individual muscles, tendons and joints via connective tissue) therefore we found that the injection sites are best described by their relationship to the nearby cutaneous projections, whose receptive fields are very discrete and easily specified.

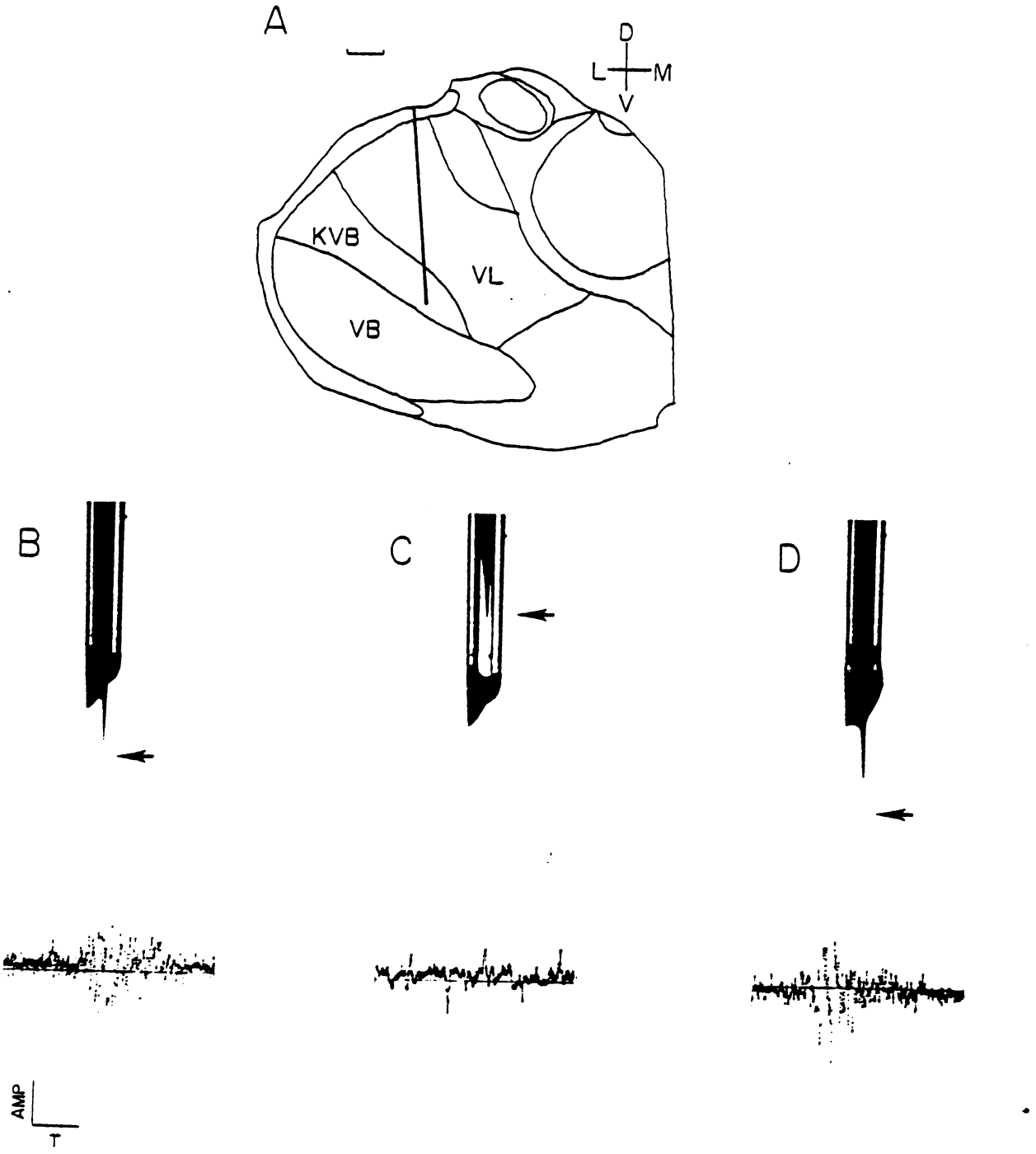
Thirteen injections were attempted using the injecting electrode. Most animals received bilateral injections as there are few ipsilateral medullo-thalamic projections from the dorsal medulla (Ostapoff & Johnson '83b). Six of these injections resulted in what was considered kinesthetic specific labeling. That is, only the kinesthetic regions of the dorsal medulla were labeled. Three other injections resulted in substantial labeling of cells in the cDCN and were used to confirm the results of the kinesthetic specific injections. In two control injections, intentionally placed dorsal (in the ventrolateral nuclear complex) to the KVB, no labeled cells were found in the dorsal medulla while cells in the deep cerebellar nuclei were labeled.

Two kinesthetic specific injections were made in the rostral and lateral portion of the forelimb KVB (cases 530RT and 533LT), close to the cutaneous representation of the hindlimb and ulnar hand digits 4 and 5 (see Figure 2.1). Three kinesthettic specific injections were located more medially (animal 510R, 515, and 541LT) in close proximity to the cutaneous representation of the face and the radial hand digits 3 and 2). One, rather larger injection was located in the rostral pole of the KVB. Figure 2.2 shows examples of evoked potentials recorded through an injecting/recording pipette in animal 561.

Figure 2.2 Examples of evoked potentials recorded through a recording/injecting micropipette.

A. Shown is a tracing of a transverse section through the thalamus at the level of a recording/injecting pipette track in animal 561. In this case the pipette was lowered into the thalamus until evoked potentials to stimulation of the deep tissues of the body could be detected, an injection was made and the pipette withdrawn. Bar equals 1 mm. B-D. Photomicrographs of a recording/injecting pipette are shown here (above) with examples of evoked activity (below) with the tungsten extended (B), withdrawn (C) and re-extended (D) to stimulation of the lower arm flexor muscle mass. The tip of the tungsten is indicated by the arrows. In C, the tungsten is withdrawn into the glass pipette and little neural activity is seen though a prominent 60 cycle noise is present. AMP equals 100uV; T equals 10 msec.

Figure 2.2



Rostrolateral Injections

Both injections made into the rostrolateral portion of the KVB resulted in essentially identical patterns of labeled cells in the dorsal medulla. Figure 2.1 shows one case (533LT) in the injection site was located at a recording locus responding best to wrist and digit extension and lying just ventral to a response to deep pressure into the ulnar lower arm near the elbow. The highest number of labeled cells were observed in the contralateral n x-r (83% of all the labeled cells) with an additional small cluster of large labeled cells (10%) in the medial most tip of the MT lying just ventral to the rCu-rGr border. As is evident from Figure 2.1, only 5 cells outside of these two nuclear subdivisions were observed to contain label in the sections plotted. The other rostrolateral injection (530RT, not shown) was made at a recording locus responding best to ulnar digit flexion and tapping into the dorsal wrist. This locus was situated ventral to the hindlimb KVB and dorsal to the distal glabrous D4 projections. In this case 44% of all the labeled cells were observed in n. x-r, 3% in the most medial portion of the MT with 40% of the labeled cells located in the Gracile nucleus (clustered in the ventral portion). Only one labeled cell was observed in the ECu and one in the bCu in this animal.

Medial Injections

The most caudal medial injection (515) was located in the forelimb KVB just lateral to the cutaneous face representation. The receptive field at the injection site in this case was located in the deep tissues of the radial forelimb. The distribution of labeled cells in

the dorsal medulla is shown in Figure 2.3. Approximately one half of the labeled cells were located in the bCu (19 of 37) and the other half (18 of 37) in the medial ECu and adjoining lateral part of the MT. No cells were labeled in cg x-r.

Another medial injection, also with a responsive loci to stimulation of the deep tissues of the lower arm (510R, not shown) was located over the projections from the claw of D3 of the hand and approximately one mm rostral to the cutaneous palm pads B and C. This injection resulted in labeled cells located primarily in the bCu (25%, 32 of 126), ECu (33%, 42 of 126), and lateral MT (18%, 22 of 126).

The third kinesthetic specific injection (541RT) made into the medial portion of th KVB was made into a locus responding to stimulation of the deep tissues of the lower arm located over the cutaneous digit 2 projections (Figure 2.4). Again labeled cells were observed primarily to lie within the bCu, ECu and MT. In this case approximately two thirds of the observed labeled cells were in the bCu (81/120), 20% in the ECu (23/120) and 10% in the MT (11/120). In this case 10% of the labeled cells were found to be in the rostral layer VI of the spinal cord. This animal was one of those whose medulla was mapped on the fourth day following injection of the KVB.

Injection into the rostral pole of the KVB

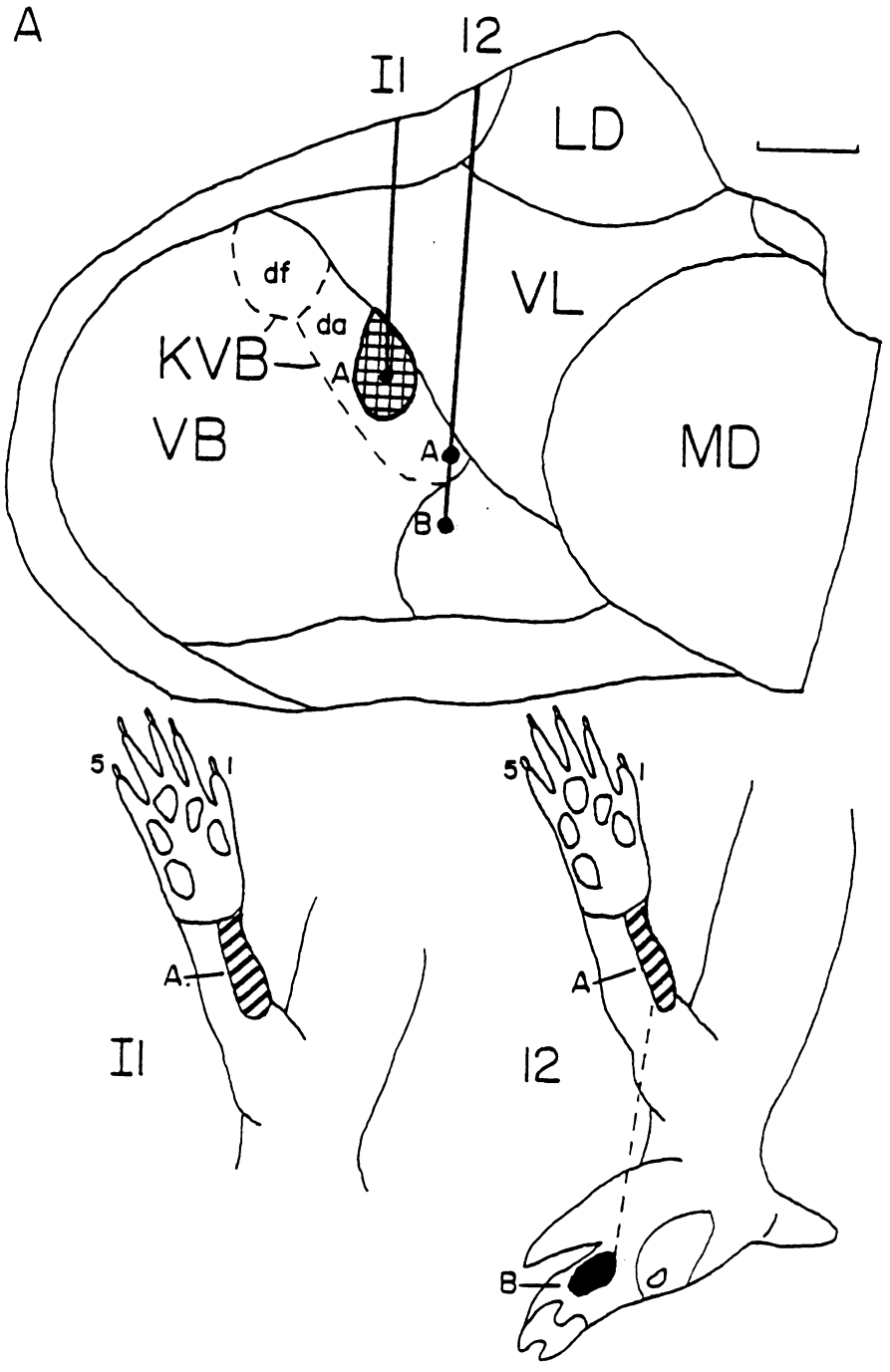
A rather large injection was made into the rostromedial pole of the KVB in one animal (541 LT) at the level in which there are no underlying cutaneous projections, rostral to the cutaneous projections from the radial digits and medial to the cutaneous projections from the

Figure 2.3 Injection into the caudomedial KVB.

A. This figure is the caudalmost injection made in this study and was within the caudal 1.0 mm of the rostral KVB region (case 515). The mapping penetration medially (P 12) encountered projections in the KVB from the radial lower forearm (A) dorsal to projections from the mystacial vibrissae (B). The injecting electrode (I1) was lowered 300 um lateral to this until responses were recorded from stimulation of the deep tissues in the radial forearm (A). Bar equals 1 mm. B. Low power photomicrograph illustrating this injection site. The ventrobasal cell lobules are located ventral to the injection site. Also seen in this photomicrograph is the portion of a pre-injection electrode track (P12). Box denotes area enlarged in C and D. This is a DAB-thionine counterstained section. Bar equals 1mm. C. This is an enlargement of the area indicated in B. The typical dense core/halo appearance of the HRP injection site when reacted with DAB can be seen. To the upper right is the pre-injection electrode track illustrated in A. The arrangement of the blood vessels near the injection site (arrow) may be used for orientation in D. Bar equals 0.5 mm for C and D. D. This is a section adjacent to those shown in B and C but reacted with TMB and left uncounterstained. Note the same blood vessels as seen in C. The extent of the TMB reaction product as seen here is larger than the halo of the DAB reacted section in C. It is important to note that all the injections reported in this study were drawn using the TMB reacted sections in order not to underestimate the size of the injection sites. E. A large triangularly shaped labeled cell in the Mt resulting from the injection shown in A-D. The location of this cell in the medulla is shown in F. Scale bar equals 50 um.

F. Distribution of labeled cells in the dorsal medulla following HRP injection shown in A. Roughly equal numbers of cells were observed in the bCu as in the ECu and Mt combined in this case. No labeled cells were observed in cCu, cg x-r nor in Layer VI of the rostral spinal cord. Arrow indicates location of the labeled cell shown in E. Scale bar equals 1 mm.

Figure 2.3



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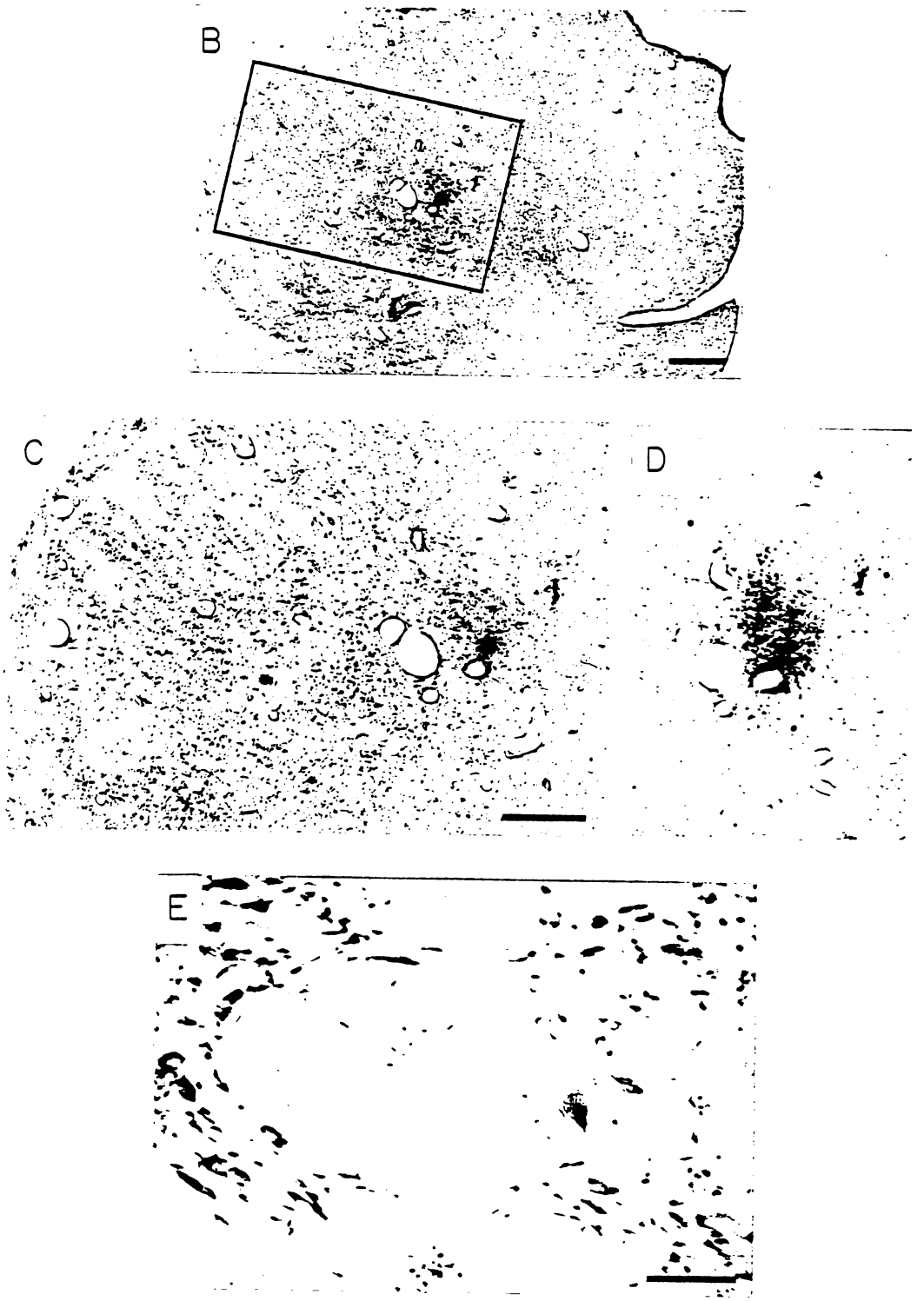
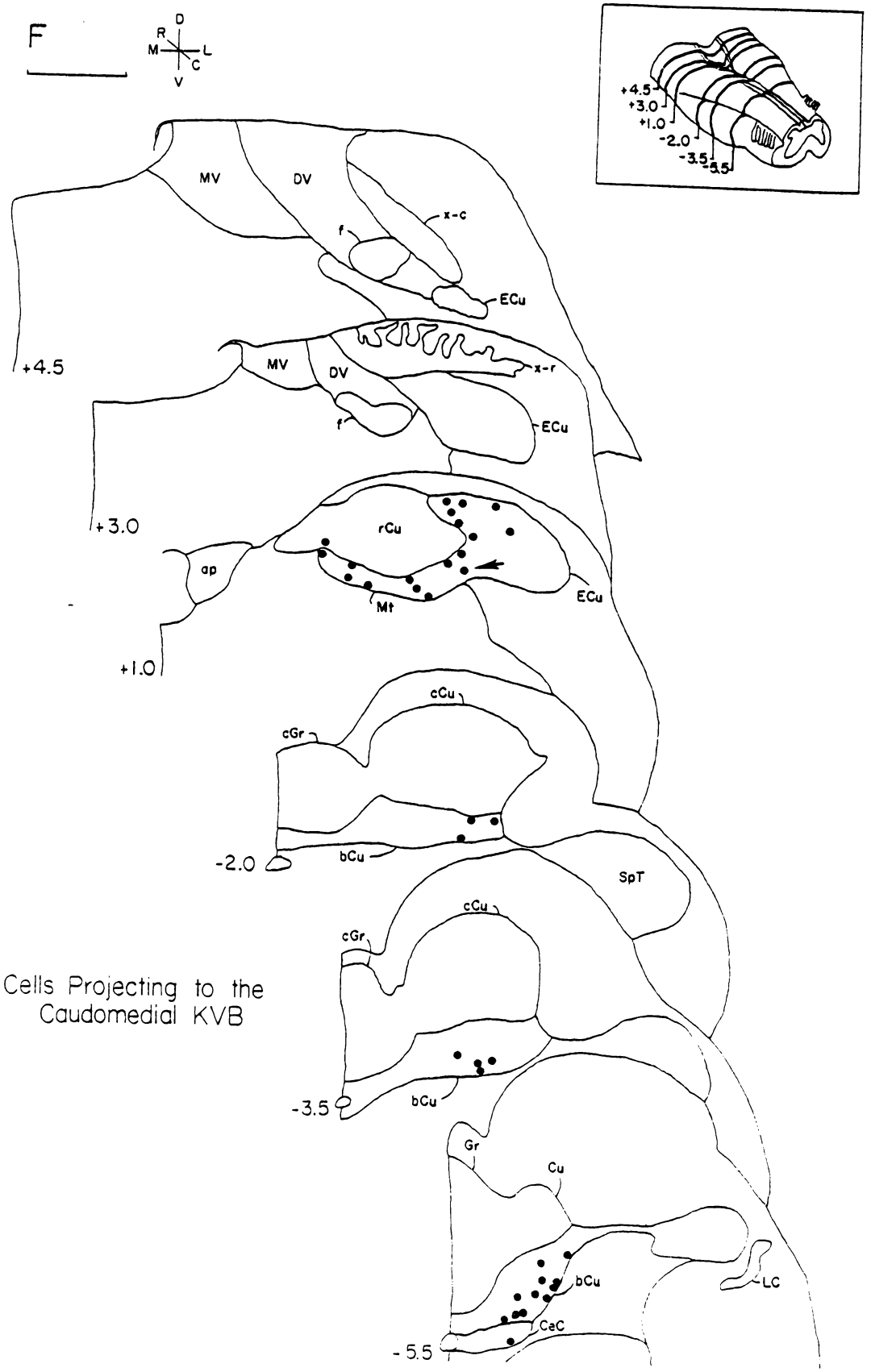


Figure 2.3



Cells Projecting to the Caudomedial KVB

Figure 2.4 Injection in the medial KVB.

A. This figure (case 541 RT) is similar in format to Figure 2.3 At the top is a drawing of a transverse section at the maximal extent of the injection site in this animal (I2). Two of the electrode tracks from the pre-injection map were located lateral to the injection site. Pre-injection penetration 5 (most lateral) traversed the portion of the KVB receiving projections from the hindlimb and axial body (df) dorsal and post-axial forelimb (da) and the glabrous projections from digit 4 (D4) most ventral. Penetration 6 encountered forelimb projections to the KVB, including extension of the radial digits (B and D) as well as the projections from the glabrous representation from the digits 3 (E) and 2 (F). The injection (penetration I2) was made into the projections from the deep tissue of the radial forearm above the distal glabrous D2 representation. This injection site was approximately 500 um in both the ML and AP planes but much longer in the DV direction. The dorsal most portion of this injection site was into a part of the ventrolateral nucleus receiving projections from the contralateral n. lateralis and interpositus as shown by labeled cells in sections through the cerebellar deep nuclei (not shown). B. Distribution of labelled cells in the dorsal medulla following HRP injection into the medial KVB. In this case the injection site was located in the KVB over the representation of the distal glabrous surface of the second digit of the hand which places this injection site rostral to that in Figure 2.3. The majority of labelled cells in the medulla contralateral to the injection in this case were observed in the medial two-thirds of the ECu, lateral three-fourths of the Mt, and throughout the bCu. Some few cells were observed in the extreme rostral portion

of layer VI of the spinal cord (levels -3.5 and -5.5) and three were observed in n x-r., rostrally. Since this animal received bilateral injections of HRP (see Figures) and n. x-r appears to contain small numbers of cells projecting to the ipsilateral thalamus (see other paper) these may be cells labeled from the ipsilateral injection which heavily labeled the cells in cg x-r on the contralateral side.

Figure 2.4

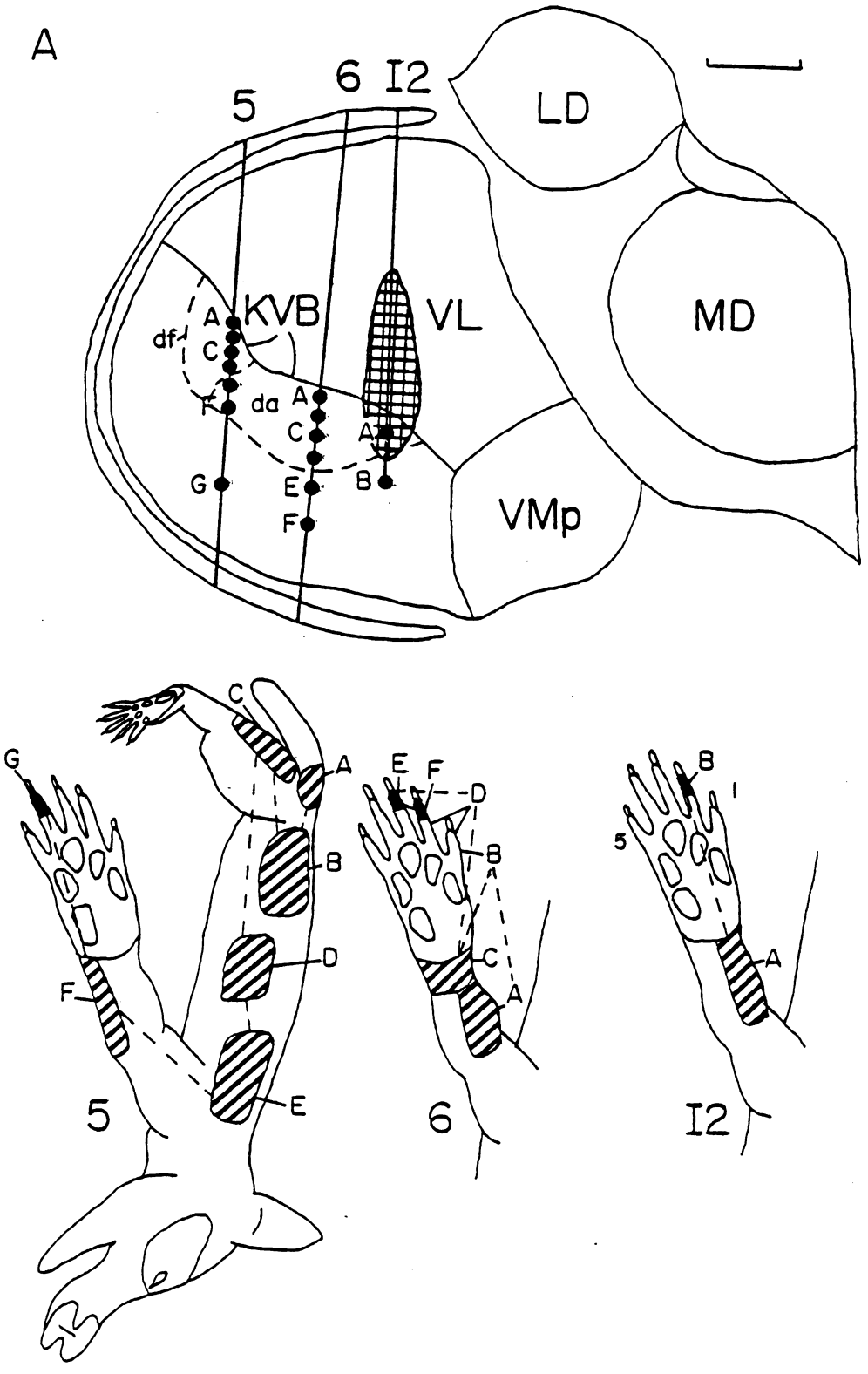
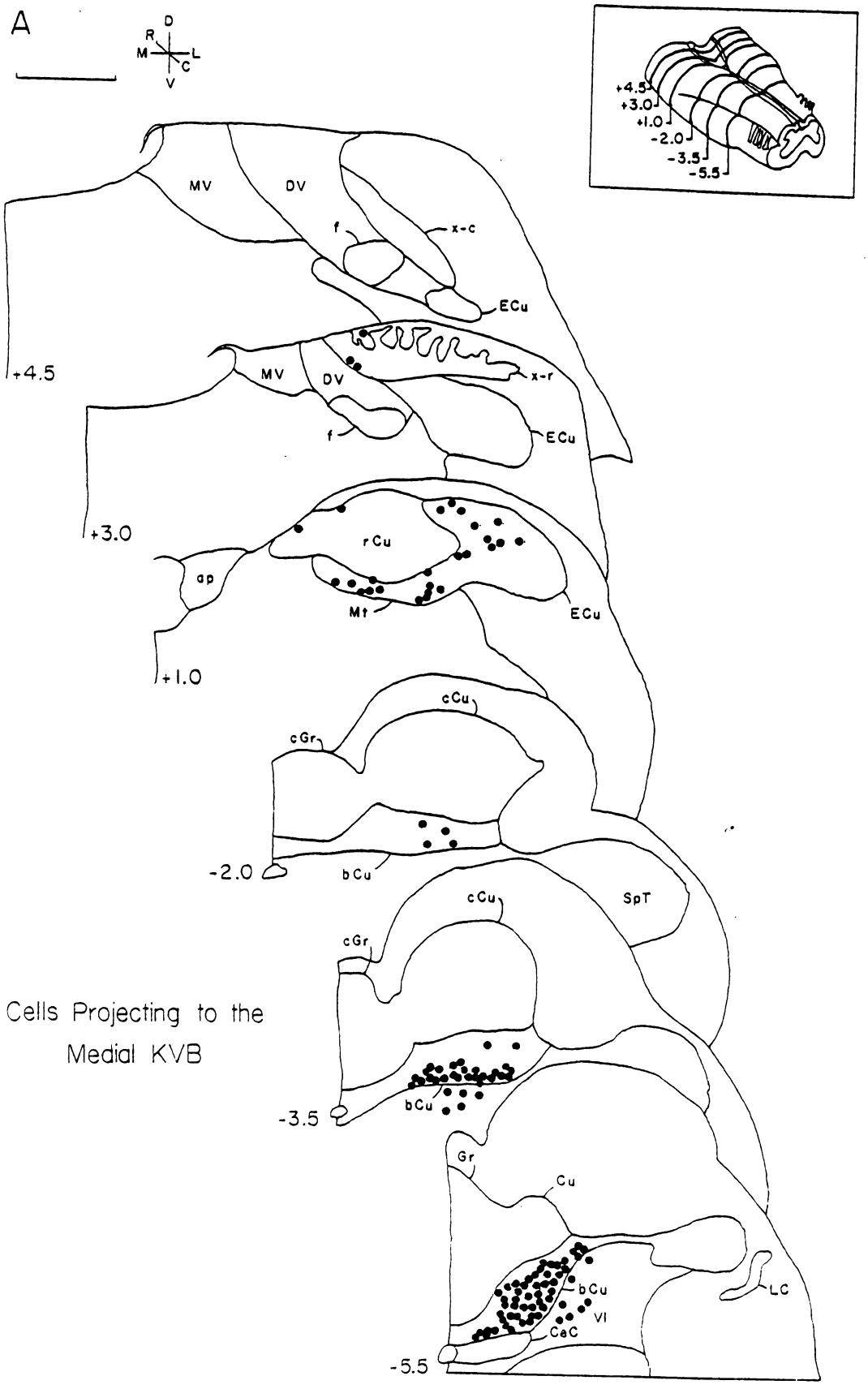


Figure 2.4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Cells Projecting to the
Medial KVB

ulnar digits. This injection was made into the region of two loci, one responding to extension of digits 2-4 of the hand and the other (800 um more dorsal) to stimulation of the deep tissues of the lower forearm. The injection site is shown in Figure 2.5 A and the resulting labeled cells observed in the dorsal medulla are shown in Figure 2.5 B. 46% of the observed labeled cells were found in the bCu (113/244), 9% in the ECu-MT (22/244) and 30% in the cg x-r (74/244). This was another animal whose medulla was mapped on the last survival day before perfusion (see Figure 2.9).

Figure 2.6 presents a summary of the results of the medial and lateral injections into the KVB. There was virtually no overlap in the distributions of cells projecting to the lateral KVB (triangles) and that of cells projecting to the medial KVB (circles) except perhaps in the extreme medial tip of the Mt extension of the ECu (arrow).

Other Medullary Projections to the KVB

Cells in the infratrigeminal nucleus (IFT, Berman '68) project to the KVB. In every case in which cells in the dorsal medulla were found to contain HRP, a few cells in the IFT also were HRP positive. No differences in the distribution of labeled cells was observed following injection into the medial as opposed to the lateral portions of the KVB.

Labeled cells were also occasionally observed in the lateral cervical nucleus (LCN) and in the rostral portion of layer VI of the spinal cord. These projections were however quite inconsistent with respect to the location of the injection site. One of the injections into the medial KVB (541 RT) resulted in labeled cells in these areas.

Figure 2.5 Injection near the rostral pole of the KVB.

A. This rather large injection (case 541 LT) was made into that portion of the KVB near near the most rostral level from which we could evoke responses to peripheral stimulation (Wiener et al. '82), rostral to projections from the glabrous skin of the radial digits of the hand. Note that penetration 3 encountered projections to the KVB from the lower axial body (A) and the digits of the foot (B) while penetration 4 and I1 traversed only forelimb kinesthetic projections. The injecting electrode was advanced through the entire dorsoventral extent of the responsive field (KVB) at this level and encountered no cutaneous projections. Bar equals 1 mm. B. The distribution of the labeled cells in the dorsal medulla in this case is shown in this figure. Labeled cells were observed in all the regions shown in the previous examples (Figures 2.1, 2.3, 2.4, except CeC) with most of these in cg x-r and the bCu. A small number of cells were also observed in the cCuGr and the rCu, presumably resulting from HRP spreading into the rostral portions of the cutaneous projections in the lobule region of the VB. As one might expect from the spread of the injection site dorsally there were large numbers of cells labeled in the deep cerebellar nuclei in this animal. Bar equals 1 mm. C. photomicrograph shows four of the labeled cells in the cg x-r resulting from the injection shown in A. Three of these are heavily labeled (arrows) and the other more moderately labeled (double arrow). Bar equals 50 um.

Figure 2.5

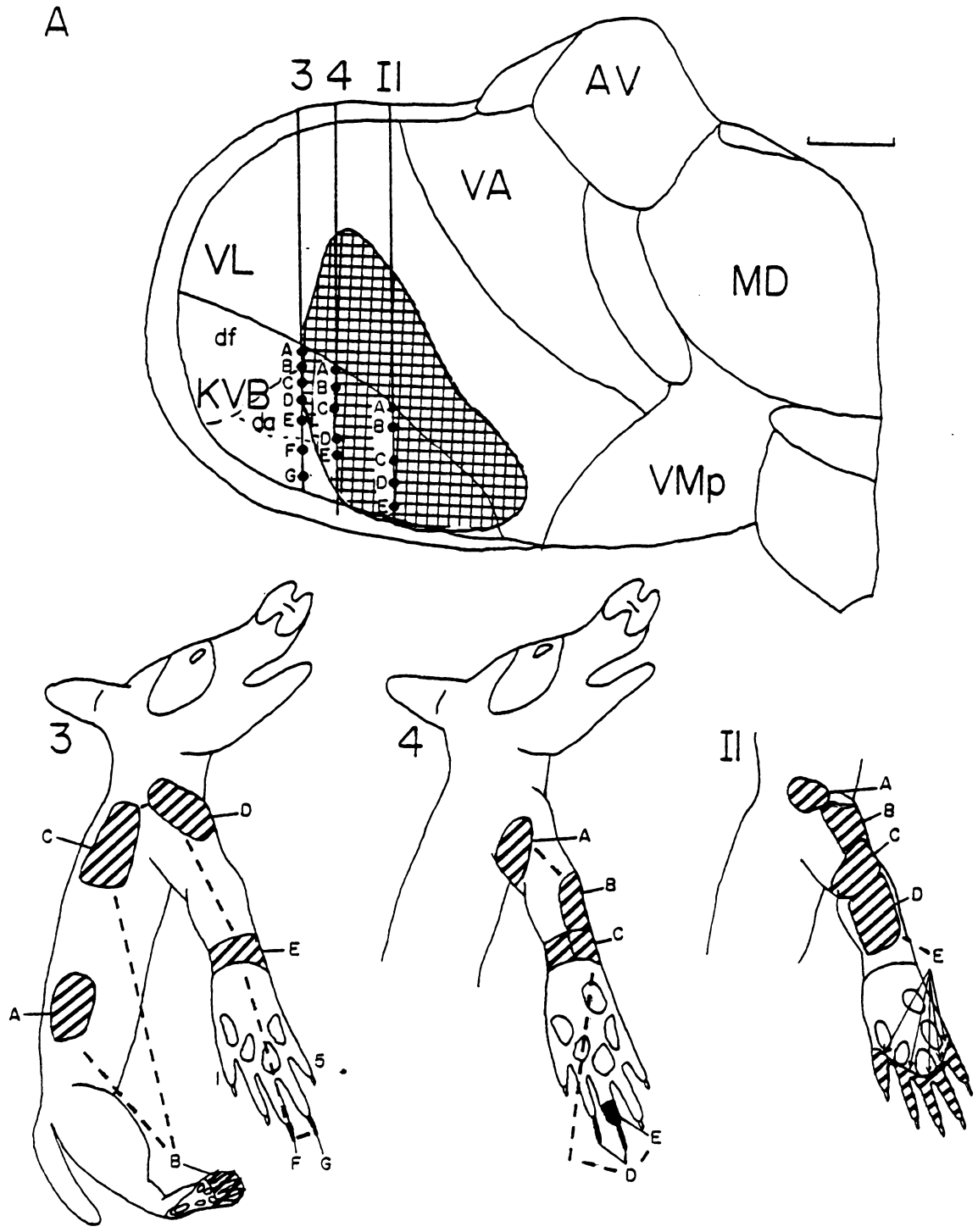
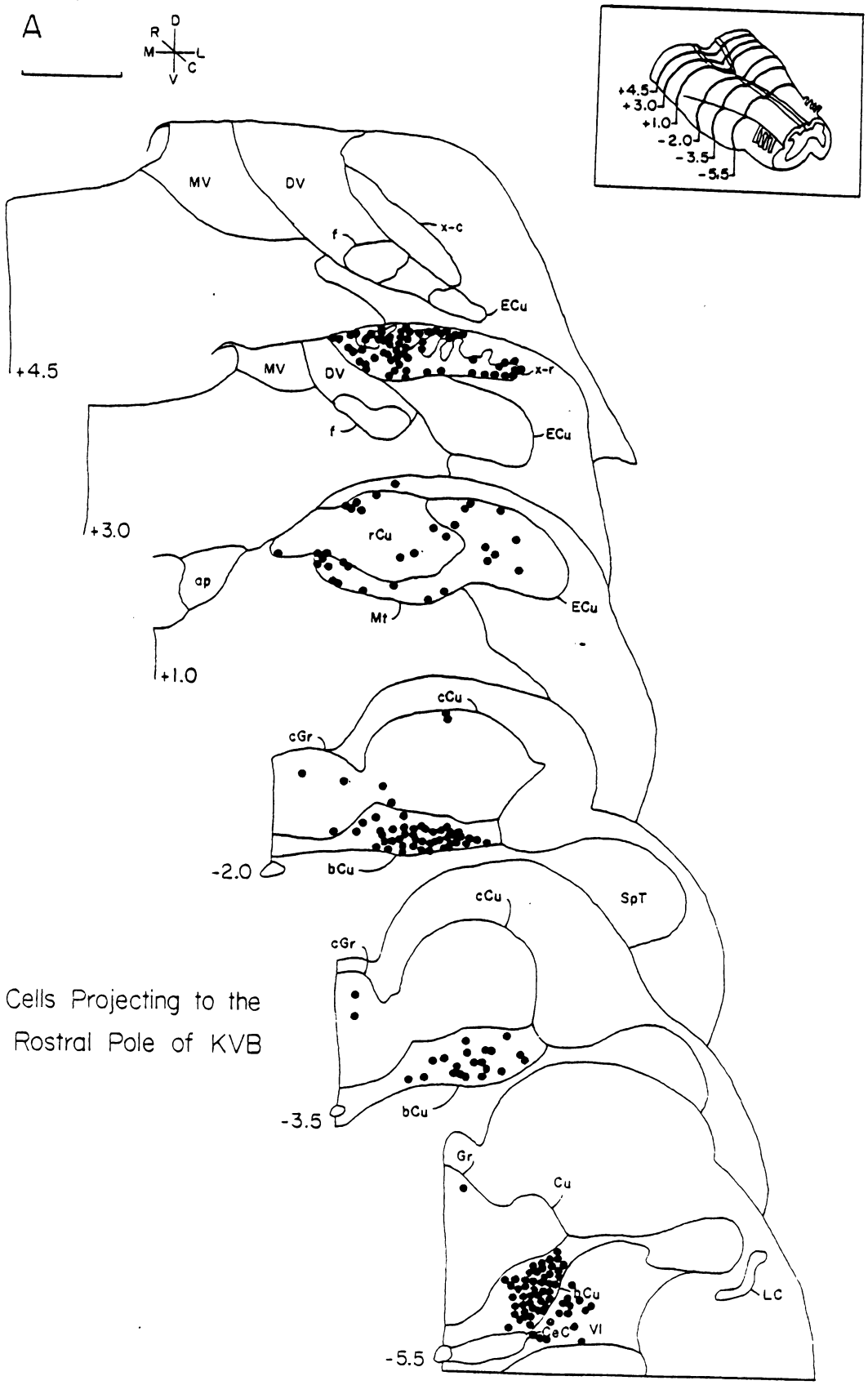


Figure 2.5



Cells Projecting to the Rostral Pole of KVB

Figure 2.5

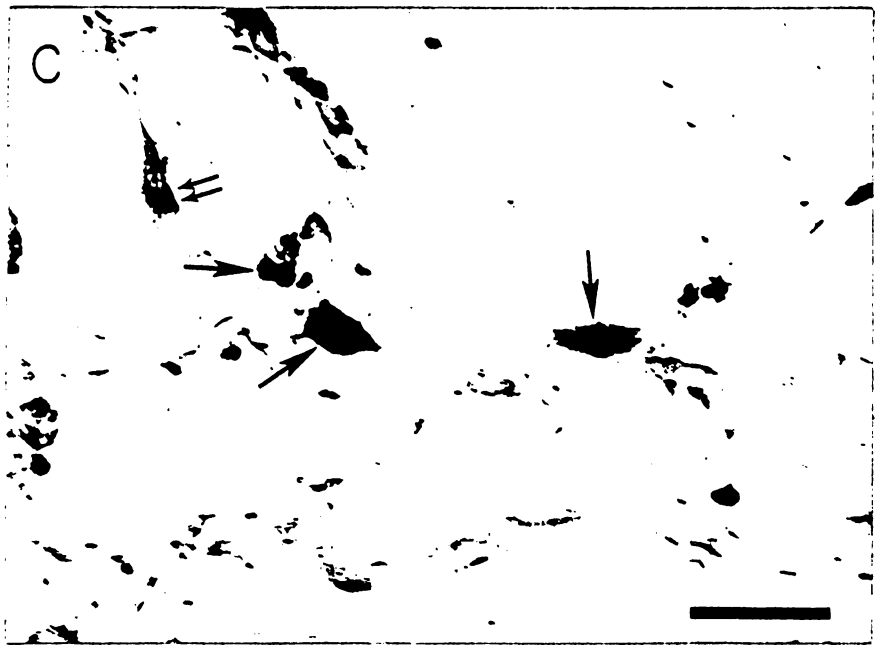
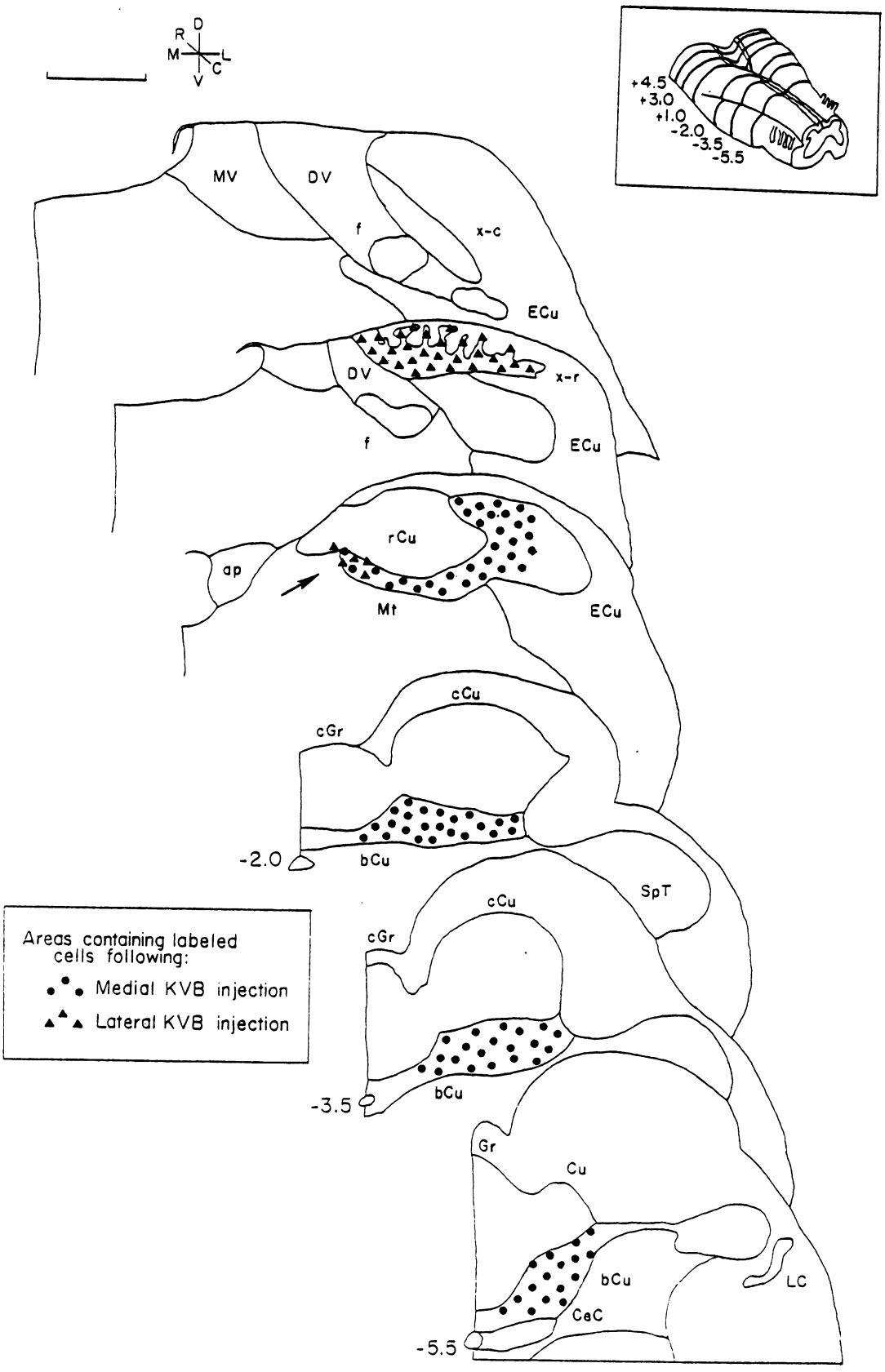


Figure 2.6 Summary of dorsal mechanosensory medullary projections to the KVB.

The distribution of labeled cells in the dorsal medulla following lateral KVB (triangles) and medial KVB (dots) are summarized in this series of standardized transverse levels. Injections into the lateral half of the forelimb KVB (overlying the cutaneous representaiton of the distal glabrous surfaces of digits 4 and 5 of the hand and medial to the cutaneous and deep representations of the foot and leg) result in heavy labeling of the cell in the cg x-r. In addition, a few cells in the medial most tip of the Mt subdivision of the Cu are usually also labeled (arrow). Whether these cells are indeed a part of the Mt (as defined by receiving projections from the deep tissues of the forelimb by Johnson et al. ('68) is not clear. Injections into the medial half of the KVB (overlying the cutaneous representation of the distal glabrous surfaces of digits 1-3 of the hand and just lateral to the cutaneous representation of the face) result in labeling of cells in the medial two-thirds of the ECu, the Mt, and the bCu. The number of labeled cells in the bCu increases, relative the that in the ECu and Mt, with increasingly rostral placement of injections into the medial KVB. Bar equals 1 mm.

Figure 2.6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Areas containing labeled cells following:
Medial KVB injection
Lateral KVB injection

In two of the three lateral KVB injections, we also observed labeled cells in the LCN or layer VI of the spinal cord.

The injection into the rostral pole of the KVB (541 LT) also involved a portion of the VL as indicated by substantial numbers of labeled cells in the deep cerebellar nuclei and also labeled a few layer VI cells (see Figures 2.4, 2.5). One of the two rostrolateral injections (530 LT) also involved the ventral portions of VL and labeled cells in the spinal cord were observed in this case. One of control injections, deliberately placed into the Ventolateral nucleus, dorsal to mechanosensory projections (549, not shown), made in these experiments also labeled substantial numbers of cell in the deep cerebellar nuclei but none in the spinal cord. One injection made into the lateral KVB (533 RT) no labeled cells were observed in either the deep cerebellar nuclei or the spinal cord.

Medullary Mapping Data

In four animals (533, 541, 549 and 561), rows of electrode penetrations were made on the third or fourth day following injection of HRP into the KVB. The penetrations were intended to traverse two subnuclei of the dorsal medlula in which labeled cells were observed following injection of the KVB , the bCu and cg x-r. The ECu and Mt have already been shown to receive kinesthetic projections but the bCu and cg x have not been mapped in raccoons. Figure 2.7 shows a reconstruction of electrode tracks traversing the bCu and the locations of electrolytic lesions made at responsive loci indicated in the figurine drawings. Note that the medial most lesion (P7) was made just ventral to the kinesthetic responses and the lateral lesion (P9) was

Figure 2.7 Mapping data through the bCu.

A. A reconstruction of a row of electrode penetrations through the bCu at a level shown in the inset (animal 533 LT). The responses recorded in those portions of the electrode tracks traversing the cDCN show the typical cutaneous body somatotopy reported earlier (Johnson et al. '68). Ventral to this cutaneous body representation, in the bCu are recorded responses from projections of the deep tissues of the forelimb (P 9D,E, and F; P 8D-G and P 7D-F). Microlesions were made at P 9F (responding to kinesthetic stimulation of the head of the humerus) and in p7 in between loci C (responding to stimulation of the glabrous skin over the distal digit 1 of the hand) and D (responding to extension of the radial digits 1 and 2 of the hand). These lesions were observed to lie at the ventral and dorsal borders of the bCu (see 6B). The HRP injection made into the contralateral KVB of this animal and the resulting label in the medulla is shown in Figure 2.1). Bar equals 1 mm. B. This figure shows one of the lesions (arrow) made at a level approximately 1.5 mm caudal to the obex, used to verify the electrode tip location in animal 533. Note that the lesion is near the ventral border of the cCu and just dorsal to the region called bCu in this study. Another of the penetrations in this row (double arrow) can be seen in this section (penetration 8 in 6A). This section was reacted with DAB and counterstained with thionine. Bar equals 1 mm.

Figure 2.7

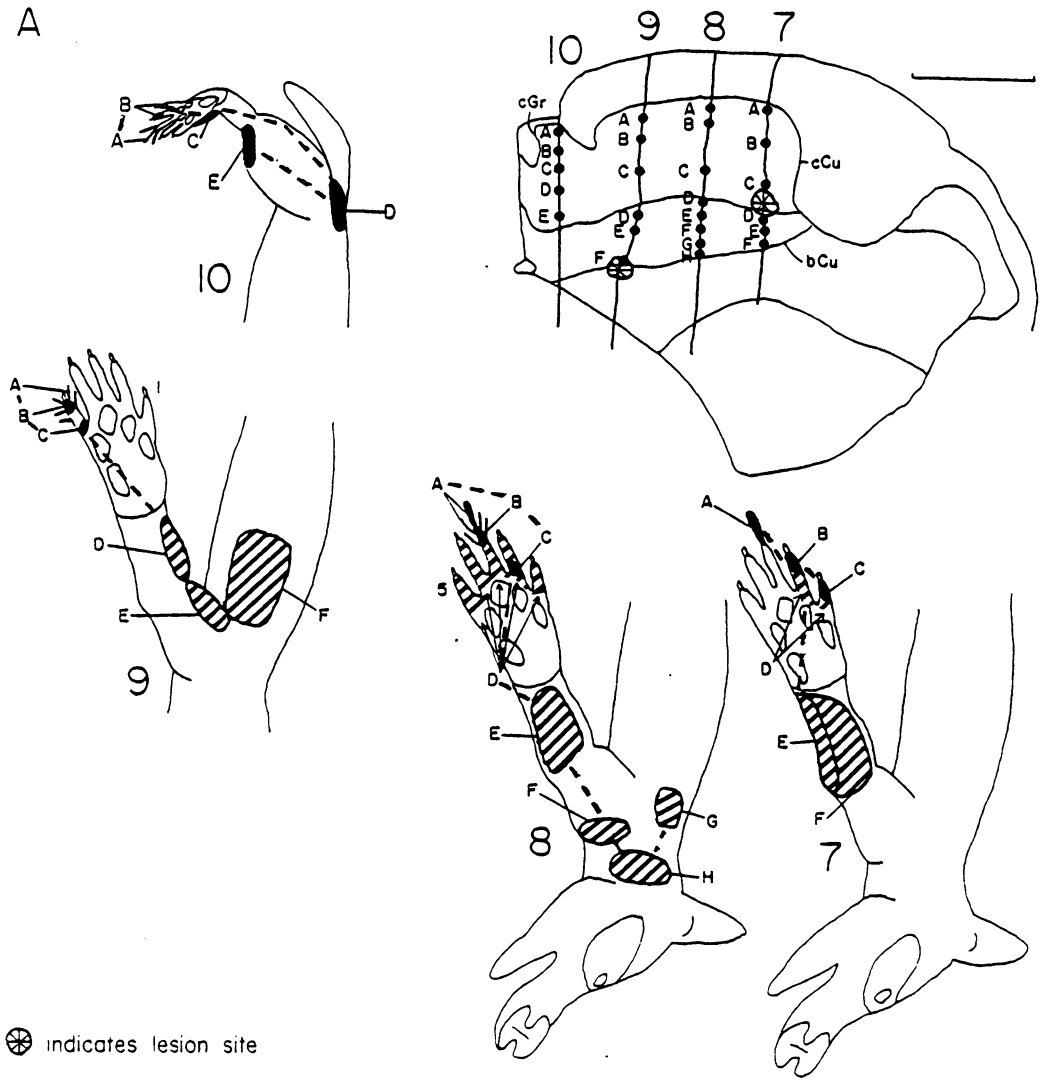
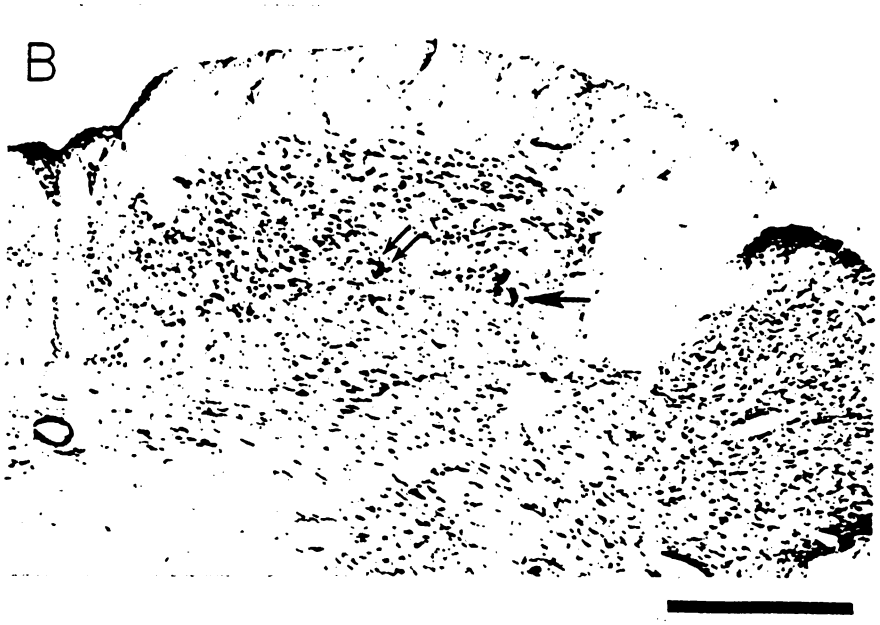


Figure 2.7



ventral to the kinesthetic responses and the lateral lesion (P9) was made just dorsal. These lesions were observed to be on the ventral and dorsal border of the bCu respectively. The injection made into the contralateral KVB in this animal was one of those which failed to transport HRP.

Figure 2.8 shows a similar reconstruction for a row of penetrations across the entire medulla at the level of the bCu and the responses encountered by the recording electrode. Again responses located in the bCu were all evoked by stimulation of the deep tissues of the forelimb and these lay beneath the cutaneous representation of the body found in the cDCN. In this animal injections made bilaterally into the KVB both transported label to the bCu (see Figure 2.4 for the left medulla as shown here and Figure 2.5 for the right medulla). Figure 2.7 B shows a part of an electrode track in the vicinity of labeled bCu cells in the region indicated here by the box.

Figure 2.9 shows reconstructions similar to those in Figures 2.7 and 2.8, this time at the level of cg x-r. The location of a lesion made just ventral to the kinesthetic projections from the hindlimb is indicated both in the camera lucida drawing (showing electrode tracks,lesion and labeled cells in this and the 2 adjacent sections) as well as in the figurine drawing below.

Figure 2.10 shows examples of evoked potentials recorded in the medulla in animal 561.

Figure 2.8 Mapping data through the bCu in the vicinity of labeled cells resulting from kinesthetic specific injections of HRP into the KVB.

A. At the top is a reconstruction of a row of electrode penetrations traversing the DCN at a level similar to that in Figure 2.7 in animal 541. This animal received HRP injections bilaterally into the KVB (for injection sites and distribution of labeled cells in the dorsal medulla see Figure 2.4 for the right medulla as shown here and Figure 2.5 for the left). Again recording loci in the cCuGr show the typical cutaneous somatotopy while those loci located in the bCu show projections from the deep tissues of the forelimb. Locus 31B is a response to stimulation of the deep tissues of digit 5 of the foot. Similar responses to stimulation of the deep tissue of the caudal body, located in the ventral portions of the Gracile nucleus have been previously reported in cats (Dykes et al. '82) and tree squirrels (Ostapoff et al. in press). Box around locus 30C indicates the area shown in B. Bar equals 1 mm. B. Photomicrograph of penetration 30 (upper right) through the caudal bCu (approximately 2.5 mm caudal to the obex) in the vicinity of three labeled cells (arrows) from a medial KVB injection (animal 541RT, section 134). This penetration encountered responsive loci to stimulation of the distal glabrous digit 3 of the foot dorsal; extension of the lateral (4 and 5) digits of the foot intermdiate; and the deep tissues of the lower arm at approximately the level shown in this figure. Bar equals 100 um.

Figure 2.8

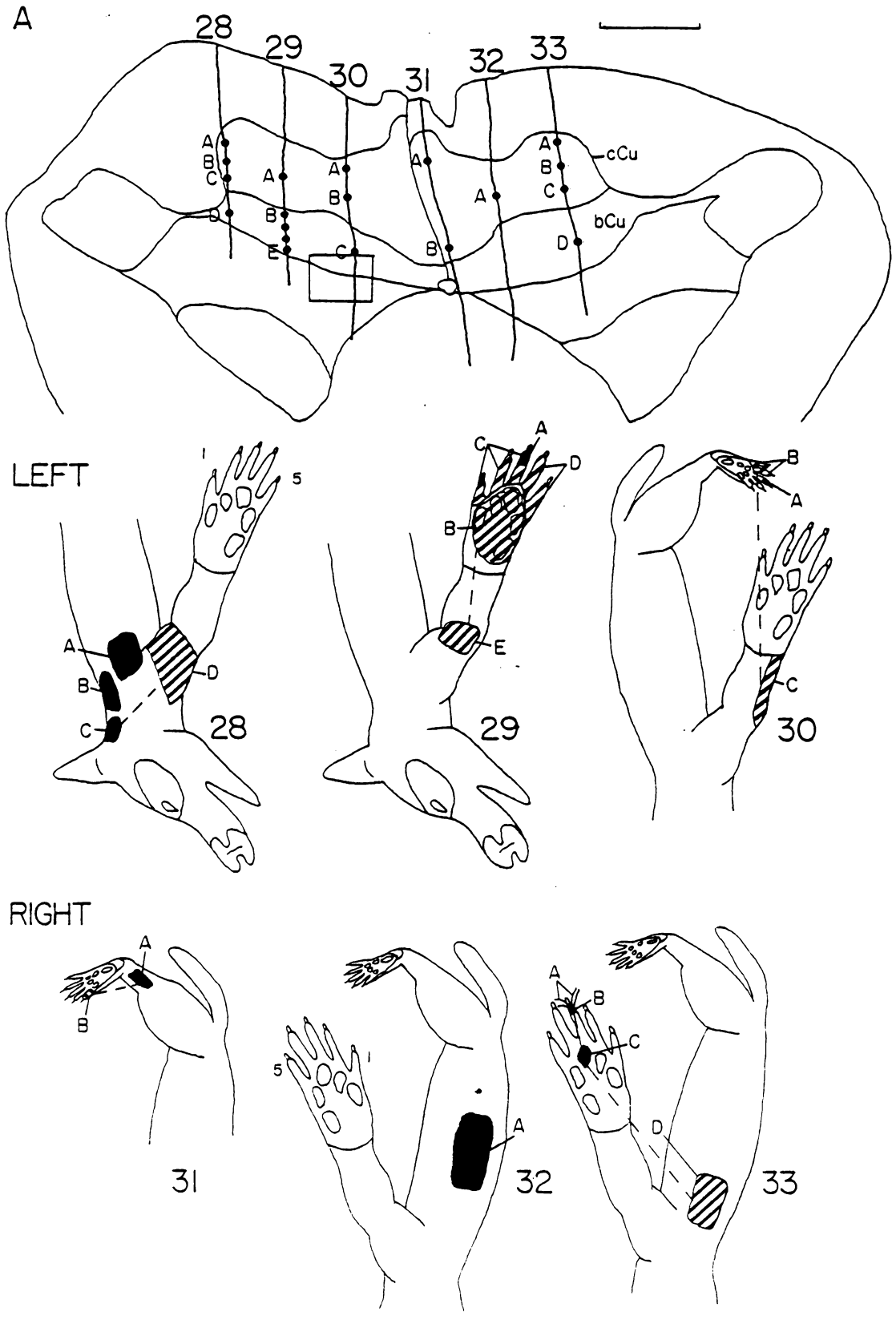


Figure 2.8

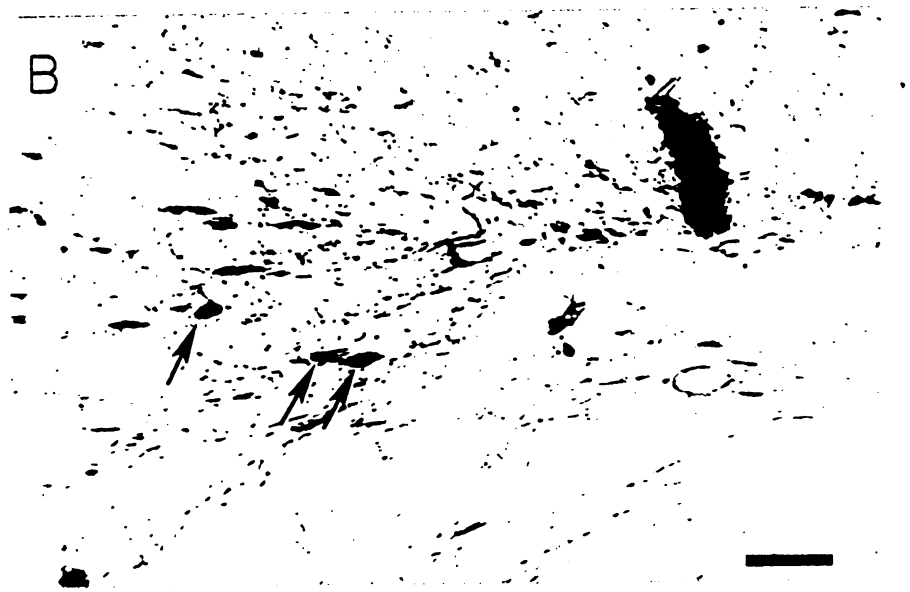


Figure 2.9 Mapping data from cg x-r in proximity to labeled cells from a kinesthetic specific injection into the lateral KVB.

At the top is a reconstruction of electrode penetrations traversing the reticular portion of cg x (case 541 LT). Responsive loci are indicated along the electrode penetration reconstructions. All the labeled cells in the section through the dorsal medulla showing electrode tracks within cg x-r and the adjacent 2 sections are indicated by the triangles (see Figure 2.5 for injection site and complete distribution of labeled cells in this case). In the penetrations with responsive loci located in cg x-r (penetrations 11-13) small amplitude evoked responses to stimulation of the deep tissues of the leg or axial body were located just below the dorsal surface of the medulla. Penetration 14 was located in cg z and recorded responses to stimulation of the deep tissues of the hip and upper leg. Penetration 15 passed through the descending vestibular nucleus and no loci responsive to mechanical stimulation of the body were encountered. A lesion was made 0.5 mm below the responsive field in Penetration 11 as shown in the upper figure. The lateral two penetrations (12 and 13) also traversed the ECu and trigeminal nuclei more ventrally and typical large amplitude responses were recorded from these nuclei. Bar equals 1 mm.

Figure 2.9

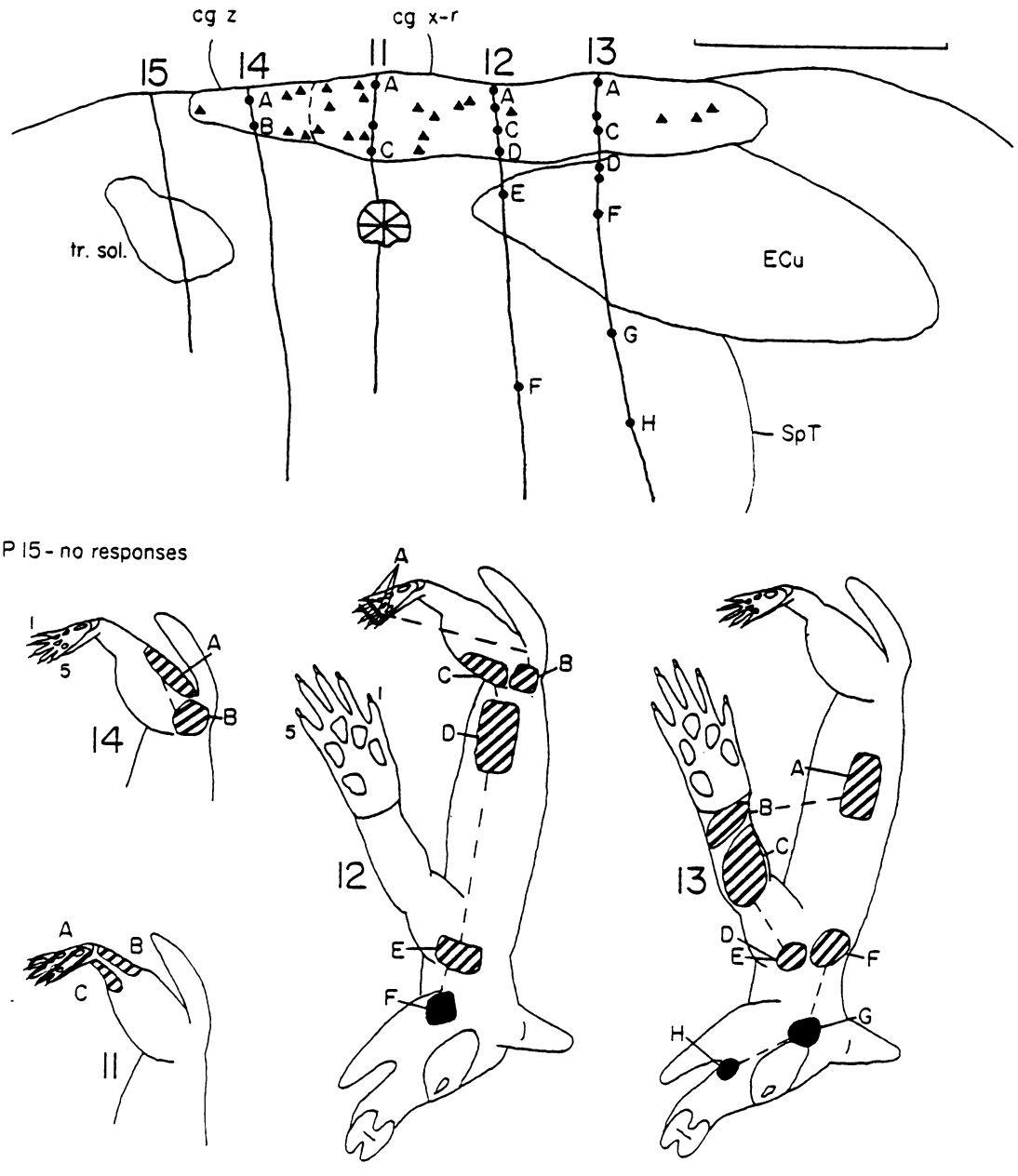
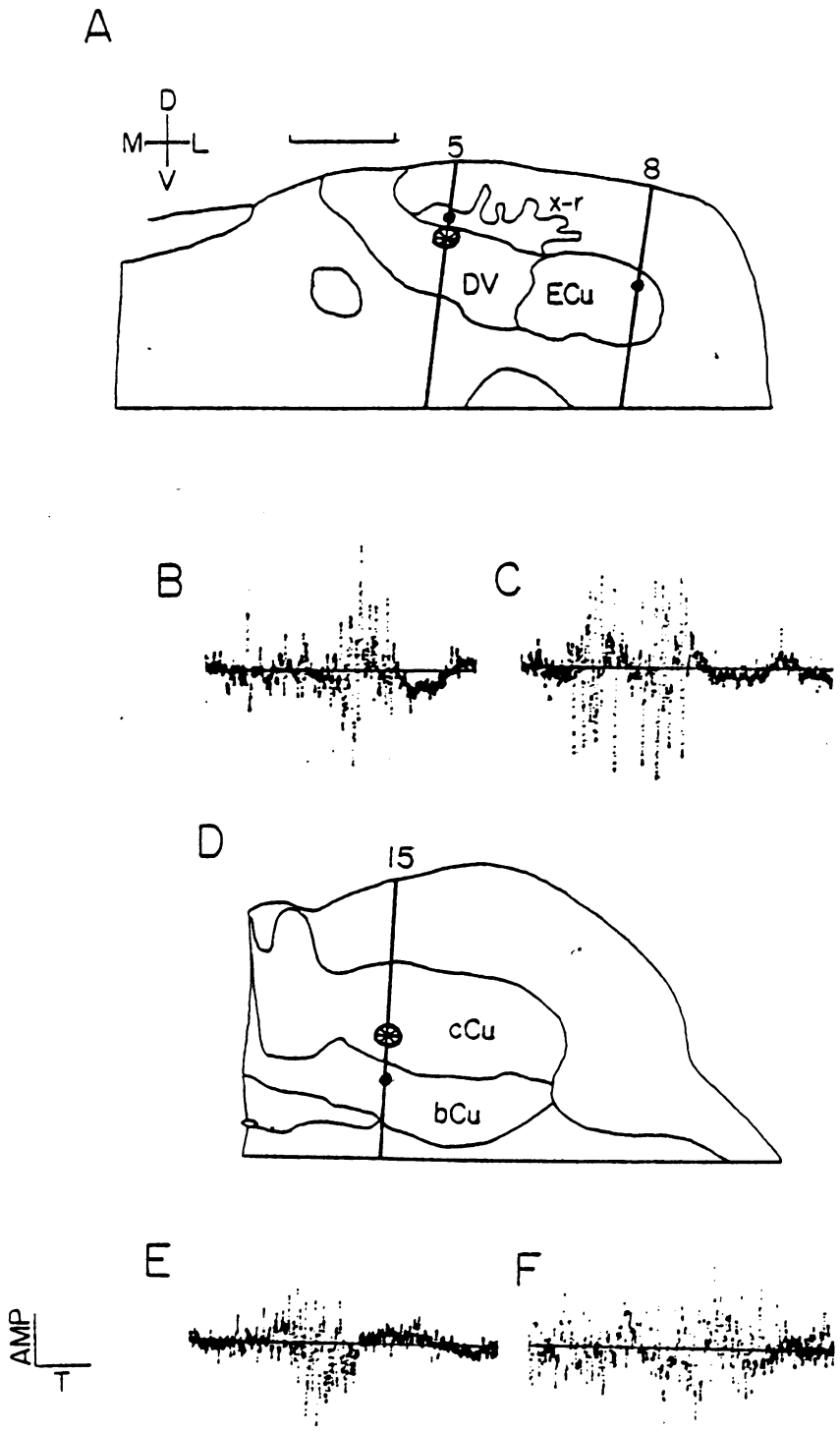

cg z
cg x-r
15
14
11
12
13
A
B
C
D
E
F
G
H
tr. sol.
ECu
SpT
P 15 - no responses
1
5
14
12
13
11

Figure 2.10 Examples of evoked potentials in the dorsal medulla.

A. This is a tracing of a transverse setion through the medulla of animal 561 at the level of the cg x-r showing reconstructions of two mapping electrode tracks (5 and 8) and the locations of a marking lesion (track 5, asterisk) and recording loci shown in B and C (dots). Bar equals 1 mm for A and D. B. Evoked potentials recorded at the indicated location in A, track 5 (dot), approximately 0.4 mm above the marking lesion. This response was elicited by a sharp tap into the dorsal aspect of the foot. Responses could also be seen to flexing the ankle and tapping the lower leg. C. Evoked potential recorded from the ECu at the location shown in A (track 8, dot). This potential was recorded following a sharp tap into the post-axial lower arm near the elbow. The response in B appears to have a rather long latency to reach full amplitude and to consist of fewer individual units than that shown in C, but we did not quantify these measures. AMP equals 100 uV; T equals 10 msec for B and C. D. This is a tracing of a transverse section, from the same animal as A, at the same magnification, but through the level of the bCu. Shown is a reconstruction of one electrode track (15) and the location of the evoked potentials shown in E (at the lesion site marked with an asterisk) and F (dot in the bCu). E. Evoked potential elicited by lightly touching the glabrous skin of pad A of the forepaw. The marking lesion was made at the location of the response. AMP equals 100 uV; T equals 10 msec. F. Evoked potential to a sharp tap into Digits 2 and 3 of the forepaw. The response shown in F, from the bCu, appears to have a longer latency to full amplitude than that in E and would appear to be smaller in amplitude (note the scale change in vertical magnification: for this record AMP equals 50 uV; T equals 10 msec).

Figure 1.10



DISCUSSION

The Kinesthetic Shell of the Ventrobasal Complex

Following the suggestions of Rose & Mountcastle ('52) that thalamic nuclear groupings should follow functional criteria where possible, we consider that contiguous areas in the ventral nuclear group of the thalamus which receive mechanosensory projections constitute the ventrobasal complex. Therefore our kinesthetic region is a subunit of the ventrobasal comples. Other subdivisions include: the lobule region (n. ventralis posterolateralis), which receives cutaneous input from the glabrous surfaces of the paws (Welker & Johnson '65); n. ventralis posteromedialis, receiving trigeminal input (Welker & Johnson '65); and the n. ventralis posteroinferior, which relays mechanosensory information to the second somatosensory cortical area (Herron '83).

The physiological organization and cytological details of the thalamic region we designate here as the KVB are discussed in detail elsewhere (Wiener, Johnson & Ostapoff '82). It may be said here that all the injection sites reported in this study were found to be located dorsal to and/or rostral to the conspicuous thalamic lobules reported to receive projections from the glabrous skin of the hand by Welker & Johnson ('65). Though it is difficult to state definitively from our material here, the injections sites involve a large cell zone located at the border between VL and the lobules of VB. This region may also be within the field of spinothalamic projections (Craig, personal comunication) in raccoons. In these respects, the KVB reported here

resembles the ventrointermediate nucleus (Vim) reported by Pearson and Haines ('81) in galago and the spinal portion of the VL (sVL) in cat (Jones & Burton '74), also called the VL-VB border zone (Berkley '80) Also this region in raccoon is much smaller in volume than reported in galago (Pearson & Haines '81) but appears larger than that region receiving fast 1A muscle afferents reported in monkey by Maendly et al. ('81). We did not observe any labeled cells in the caudal descending vestibular nucleus as reported in cat (Kotchabhakdi, Rinvik, Walberg & Yingchareon '80). We have inconclusive evidence concerning projections from the deep cerebellar nuclei to the KVB. When our injections were confined (in the dorsoventral axis) to the KVB (e.g. Figure 2.3), we saw no cell labeleing in the deep cerebellar nuclei. When the injection site clearly involved portions of the VL complex dorsal to the KVB, then we always observed cell labeling in thye ipsilateral deep cerebellar nuclei (primarily in the n. lateralis and interpositus). However considering the reservations concerning uptake and transport of HRP (Jones '75b) particularly with small thalamic injections, we can make no conclusions concerning cerebellar input to the KVB. This would require tritiated amino acid injections made into the deep cerebellar nuclei, which we have not done. Segregation of cerebellar afferents from medial lemniscal afferents has been reported in cat (Hendry et al. '79) and monkey (Tracey, Asanuma, Jones & Porter '80) and our KVB region more closely resembles the "deep" shell of the caudal part of the ventroposterolateral nucleus (VPLc) described in monkey (Jones & Friedman '82 , Jones et al. '82).

Nuclear subdivisions in the dorsal medulla of the raccoon

Previous work in our laboratory (Ostapoff & Johnson '83b) has shown that six subnuclei in the dorsal medulla of the raccoon project to the ventrobasal complex: the cDCN, bCu, rCu, Mt, ECu, and cg x-r. The present study shows that four of these project to the KVB: bCu, ECu, Mt and cg x-r. Further, comparison of the lateral (Figure 2.1) versus medial (Figures 2.3, 2.4) indicate that a mediolateral segregation of projections to the rostral forelimb KVB exists in the ascending somatosensotry system of the raccoon. The lateral portions of the forelimb KVB (closest to the cutaneous representation of the hindfoot, axial body and ulnar hand digits) receive projections primarily from cg z and x-r and to a lesser extent, large cells located in the medial most portion of the Mt extension of the ECu. The more medial portion of the KVB (nearest the cutaneous representations of the forearm radial digits of the hand) receives projections from cells located in the medial two-thirds of the ECu, the lateral three-fourths of the Mt, and the bCu. These latter projections from the bCu also show a quantitative rostrocaudal organization (Figures 2.3-5) with proportionately more cells in the bCu being labeled following rostral injections while proportionately more cells in the ECu-Mt are labeled from more caudal injections into the medial forelimb KVB.

Mapping Data

The mapping data reported here confirms that the bCu and cg z and x-r receive projections from the kinesthetic receptors of the forelimb (cg x-r and bCu) and hindlimb (cg z) in the raccoon. The bCu was not

mentioned as receiving such projections in an earlier mapping study of the DCN and ECu in the raccoon (Johnson et al. '68). Perhaps this was due to the very different nature of the effective stimulus (deep tissue versus cutaneous light touch) and the abrupt shift in somatotopy at the cCu-bCu border. That is, cells in the ventral cCu respond to light touch (no visible indentation) of the glabrous skin of the digits and palm pads while the cells in the bCu respond only to large indentations of the skin and underlying tissue or joint movements of the forelimb. Unless specifically applying the latter stimuli, the bCu would remain unresponsive as recording electrodes passed through. Also the differences in the cytoarchitecture between the cCu and bCu (Ostapoff & Johnson '83b) might suggest that they not be related in terms of receiving and projecting somatosensory information. Similar kinesthetic projections lying ventral to the cCu has been previously reported in the cat (Dykes et al. '82).

The cg z and x-r have not previously been explored in the raccoon. We report here that one can record evoked responses from the region of cg z and x-r to stimulation of the deep tissues of the body though these responses differ qualitatively from those recorded in the cCu and ECu. This might be due to the small size of the cells and the relatively low density of cell bodies in these nuclei. Differences in the density of the synaptic input to these nuclei may also account for their apparently different response to stimulation of the periphery. It is also possible, using extracellular electrodes with relatively large exposed tips that we may be recording from the fibers in which the cells of the cg x-r are embedded. Physiological studies on cg z and in the region of cg x-r in cats have most often used electrical

stimulation of peripheral nerves (e.g. L&gren & Silfvenius '71) so no direct comparisons of evoked responses recorded in cg z and x-r can be made.

XZ Complex in Raccoons

Despite the "clear distinction" of cg x from cg z in the cat (Brodal & Pompeiano '57a, p. 446), in the raccoon we view these cells as forming a continuous band, caudomedial to rostrolateral, separating the nuclei of the dorsal columns (CuGr, ECu) from those of the vestibular group. This region might therefore be better designated as a complex (xz complex). In the cat, anatomical criteria have been used to segregate cgz and x (Brodal & Pompeiano '57a, b). Using physiological criteria, the distinction between cgx and cgz is less clear. Cg z is considered the primary medullary relay for hindlimb dorsolateral funicular afferents to the thalamus (Landgren & Silfvenius '71) but hindlimb muscle afferent projections have also been reported in the cg x (the caudolateral portion only) by Johansson & Silfvenius ('77c). These latter projections were found in an area of the cg x corresponding to the subregion here called cg x-r and also shown here to project to the lateral portion of the forelimb KVB. We also found hindlimb kinesthetic afferents in this region (Figure 2.8) as previously reported in the cat (Johansson & Silfvenius '77c). A better designation for the cg x-r might be the intermediate reticular portion of the xz complex (cg xz-r). A more detailed consideration of this region is currently in preparation. (Ostapoff & Johnson '83d).

Contributing Factors to these Results

Three factors may have contributed to the demonstration of segregation of projections described above. One was the use of physiologically identified injection sites. Stereotaxic placement of injections of transported markers is widely used as a means of describing projections. There are obviously individual variations in both the reference points used (skull sutures, etc.) to establish the stereotaxic planes and in the exact organization of the structures in the brain relative to these artificial planes. For instance, even using our own atlas of the organization of the VB in raccoons, we commonly must allow 1 to 3 mm of variation in coordinates when the first electrode penetration is made into the VB. Having established the coordinates of any part of the body representation in the VB then the coordinates of most other parts of the representation are easily arrived at through reference to the atlas. There is an inevitable loss of accuracy in the description of the placement of the injections in different animals when only stereotaxic coordinates are used with resultant loss of resolution when one interprets the results of such experiments (e.g. labeling distibution). We believe that the relative relationship between functional subunits within a system are more likely to remain constant between experimental subjects than the relationship between any such system and the standard stereotaxic planes. By physiologically mapping each subject before injection we were able, with a high degree of certainty to know where we were injecting. This certainity also allowed us greater confidence in comparing the results from different injection sites and different

animals with similar injection sites.

The second factor was the small size of the injections we were able to make and still observe transported label in the medulla. This was due both to the sensitivity of the chromogen TMB used in this study and the injection method employed. By limiting the size of injections we were able to specifically label not only projections conveying information from the dorsal medulla to the KVB but also to identify two projection systems within these kinesthetic projections

The third factor was undoubtedly the choice of the raccoon as an experimental model. The cutaneous projections in the ascending somatosensory system have long been known to be highly elaborated. Similar elaboration and concomitant enlargement of the nuclear areas involved in the relay of kinesthetic information from the medulla to thalamus has been exploited in this study to demonstrate modality specific projections and to a certain extent their internal organization.

Other Medullary Projections to the KVB

Due to the inconsistent labeling in the LCN and layer VI of the spinal cord it is difficult to make statements on how these projections may interact with those from the dorsal medulla. This could be remedied by studies specifically intended to address this issue using essentially the same experimental paradigm but with a more extensive selection of VB injection sites. Previous reports from cat and monkey seem to indicate substantial overlap of projections from the dorsal medulla, LCN, and spinothalamic neurons to the VB but these studies all used relatively less specific techniques (see Kalil '81, Berkley '80

and Boivie '78) The raccoon VB would seem the ideal model system to investigate this question.

Parallel Organization of Projections Between Levels in the Ascending Somatosensory System.

Though not specifically tested in these experiments, it now may be reasonably stated that within each of the three levels of the ascending somatosensory system (dorsal medulla, VB, and S1 cortex) there exist anatomically distinct subunits which receive and project different stimulus modality information. The cutaneous information has long been known to be projected to S1 from the cluster region of the DCN via the lobule region of the VB. The present studies establish that the first two levels of the projection pathway conveying kinesthetic information, from the dorsal medulla to the KVB are anatomically distinct from the cutaneous conveying nuclear regions, at least for the forelimb projections. The anatomical segregation of responses evoked by deep versus cutaneous stimulation in the S1 neocortex of the raccoon (Johnson et al. '82) makes it reasonable to postulate that the thalmocortical projections are similarly segregated, though this awaits experimental demonstration in the raccoon. Further, the present demonstration of non-overlapping projections from different medullary nuclear regions to different locations in the KVB makes the hypothesis that different functional units within what we have here termed the "kinesthetic" modality may exhibit anatomical segregation within levels of the somatosensory system and parallel projections between levels. We did not observe gross differences in the nature of the effective stimulation necessary to evoke responses in the KVB. We did observe

what appeared to be two different kinds of responses to kinesthetic stimulation. Some loci responded best to joint movement often in a slowly adapting burst. Others were more responsive to large indentations of muscle masses, often responding with a rapidly adapting bursts. There is some tendency for each of these types of responses to clustered together. The injection sites reported here as being laterally located both were made into loci responding best to joint movement and received projections form cg z and x-r. Those injections located more medially and receiving projections from the ECu-Mt and bCu were made into loci responding best to deep pressure applied to muscle masses. The rostral pole injection (Fig. 2.5) was made into an area of loci responding to both kinds of stimulation and both projection pathways were labeled. The stimulation techniques used in this study were not designed to detect such differences precisely. It would seem reasonable to investigate this question further using either dissections allowing stimulation of individual muscles and joints or perhaps electrical stimulation of the nerves supplying these extremities in order to segregate physiological categories of fibers (e.g. Type I and II afferents, etc.). It may be that each medullary subnucleus, identified here as projecting kinesthetic information to the KVB conveys information from specific receptor classes.

Parallel Processing in the Ascending Somatosensory System

Parallel processing of somatosensory information would seem to be implicated by the type of anatomical segregation of modality projections shown here. These studies do not, of course, address the issue of signal transformation, or processing, that may occur within

each level of the ascending somatosensory sytem. Interesting in this regard, is that while the main core subnuclei of the sensory nuclei in the dorsal medulla project primarily to single targets (e.g. the overwhelming majority of the cells in the cDCN project to the core or "lobule" region of the VB) there is much evidence that the output of some specific subnuclei projects to many different CNS targets. For instance, the rCu has been shown to project to a variety of brainstem nuclei as well as sparsely to the VB (cat: Berkley '80; raccoon: Ostapoff & Johnson '83b). The ECu and Mt certainly provide a major input to the somatosensory region of the cerebellar cortex (Ostapoff & Johnson '83a,b) but again, as shown here, some of the cells in these nuclei project to the KVB. Most of the cells in the bCu also may project to nuclei other than the KVB as even thalamic injections of HRP including the entire dorsal thalamus failed to label even half of the cells in this subnucleus. This suggests the possibility that subnuclei in the medulla may be processing information from a variety of receptor types related to a single stimulus modality, located in discrete body regions but for different purposes. The information relayed to other levels of the ascending somatosensory system may be relatively unprocessed (hence the paucity of interneurons in the cDCN) while information sent to other structures (perhaps in the motor efferent systems) in the CNS may show relatively more signal transformation. Certainly the possibility exists that similar kinds of input may be processed in different ways in the various subnuclei. This would require a highly sophisticated sorting system for the fibers in the dorsal column (providing the major input to the cDCN and ECu, and bCu (Albright, personal communication) and the dorsolateral columns (the major source of input to n. z and x).

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